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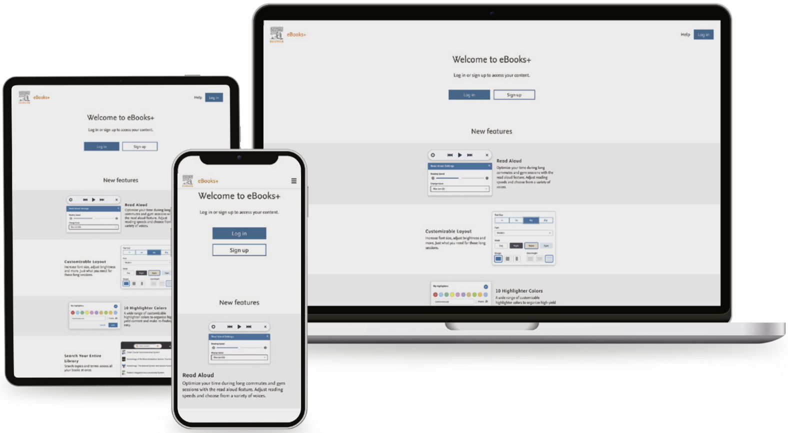

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EIGHTH EDITION

ENDOCRINE SECRETS

Edited by

MICHAEL T. McDERMOTT, MD

Professor of Medicine and Clinical Pharmacy
Lucas Family Endowed Chair in Endocrinology and Diabetes
University of Colorado School of Medicine
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I dedicate the eighth edition of Endocrine Secrets *to those who have taught me,*
those who have helped me and those who have cared for me.

First, I dedicate this to my family:
Libby, Jenny, Scott, Katie, Emily, Mac, Crystal, Hayley,
Henry, Megan, Conor, Rory, Charlie, Andy, and Ryan.

I also dedicate and give a deep-hearted thanks to my mentors:
Fred Hofeldt, Jerry Kidd, Chip Ridgway, Ken Burman,
Len Wartofsky, and Bryan Haugen.

I add a special dedication to Jan Perloff and Ken Simcic,
wonderful endocrinologists who left us far too early in their productive careers.

Finally, I dedicate this to all my patients who have honored me
by entrusting me with their healthcare and have taught me more than all my
books and all the lectures I have attended. I sincerely thank you all.

Michael T. McDermott, MD

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Preface

When I embarked on the first edition of *Endocrine Secrets* in 1992 (published by Hanley and Belfus in 1994), I could hardly have anticipated that 30 years later I would be writing and editing the eighth edition, nor could I have guessed the many significant and far-reaching changes that have occurred in our specialty during this time. I want to express my sincere thanks to all the chapter authors who have contributed to previous editions and the current one. Their generosity, experience, and wisdom have benefited many learners and patients throughout these years.

I would like to call out some chapters of particular significance. The chapter on Endocrinology in Africa, written by my dear friends, Helen Yifter Bitew and Abdurezak Ahmed Abdella, is a must-read that gives us insight into how endocrinology has developed in Ethiopia and other African countries under the leadership of great physicians such as these two. There is also a new chapter on Healthcare Disparities in Endocrinology by Dr. Rocio I. Pereira. As she points out in this very informative chapter, the amazing advances we have witnessed in diagnostic and therapeutic endocrinology are not equally available to all members of our communities, and we should strive to correct these inequities to help create a more just society for us all.

I would like to especially thank the authors of the chapters in this book for their generosity, time, and expertise to help others master the field. With each edition, I have learned an enormous amount by carefully reading each of these chapters. Their contributions benefit not only the readers but the patients those readers will care for in the future.

I have had a long and very fulfilling career in endocrinology and internal medicine. This journey has been and continues to be a joy. I have greatly enjoyed the diagnostic and treatment challenges I have encountered. I am thankful each day for my great fortune in choosing this specialty and working with the many wonderful colleagues I have encountered throughout my career.

My sincerest hope is that my fellows, residents, students, and all readers of this book will experience the same joy, enthusiasm, and fulfillment in the practice of endocrinology or its application to their particular specialty.

Michael T. McDermott, MD

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CHAPTER 1

Diabetes Mellitus: Etiology, Classification, and Diagnosis

Rebecca C. Rosenberg, Adnin Zaman, and Cecilia C. Low Wang

1. What is diabetes?

When people talk about diabetes, they are usually referring to *diabetes mellitus*, which is a term that encompasses a heterogeneous group of disorders characterized by elevated serum glucose, or hyperglycemia.

2. What is the origin of the term *diabetes mellitus*?

Although diabetes has been described in the literature as early as 1552 BCE in the *Ebers Papyrus* of Egypt by Hesy-Ra (1552 BCE), the word "diabetes" comes from the Greek word "diabainein"—described by the Greek physician, Aretaeus—and means "siphon," since people excrete excessive amounts of urine. "Diabetes mellitus" was coined by Thomas Willis of Oxford, England, in 1675, when scientists realized that the urine of people with diabetes was sweet (mellitus) rather than tasteless (insipidus).

3. What is the epidemiology of diabetes?

Approximately 5.9 per 1000 people are diagnosed with diabetes each year. Thirty-eight million Americans have diabetes. Of these, 1.3 million adults have type 1 diabetes. However, it is estimated that of the 38.4 million people with diabetes, 8.7 million are undiagnosed. The number of adults age 18 and older with prediabetes is 97 million. American Indians/Alaskan Natives have the highest rate of diabetes (16%), while non-Hispanic Whites have the lowest incidence (8.5%).

4. What is the underlying pathophysiology of diabetes?

Diabetes results from complete or relative insulin deficiency. In type 1 diabetes, which is an autoimmune disorder, the pancreatic beta cells are unable to produce insulin throughout the day while fasting or in response to carbohydrates. In comparison, type 2 diabetes occurs when individuals are unable to produce enough insulin to overcome underlying insulin resistance. Consequently, glucose is not taken up efficiently by insulin-sensitive cells to be metabolized into adenosine triphosphate (ATP). Eventually, people with long-standing type 2 diabetes may experience a marked reduction in insulin production described as pancreatic "burnout." Both types of diabetes result in high blood glucose levels; treatment is geared toward supplying or potentiating insulin production, decreasing glucose overproduction, and/or improving insulin sensitivity.

5. What is prediabetes?

Prediabetes is a medical condition that precedes type 2 diabetes. In prediabetes, people have elevated blood glucose levels but not as high as in type 2 diabetes. They are still at risk for developing other metabolic complications (fatty liver disease, high cholesterol, obesity, heart disease, and stroke) and should be screened every year for the development of type 2 diabetes. Progression from prediabetes to overt type 2 diabetes is estimated to occur at approximately 10–11% per year.

6. Who should be screened for type 2 diabetes and prediabetes?

Any person with symptoms typical of diabetes should be screened. All adults without symptoms suggestive of diabetes should be screened at age 35 and at least every 3 years thereafter. Consider screening at age 25 in people with overweight or obesity (BMI ≥ 25 kg/m^2, or ≥ 23 kg/m^2 in Asian individuals) and who have at least one of the following risk factors: first-degree relative with diabetes, history of cardiovascular disease, hypertension, elevated triglycerides, polycystic ovary syndrome, physical inactivity, high-risk race/ethnicity (e.g., Black, Latino, Indigenous American, Pacific Islander), or other physical signs of insulin resistance (e.g., obesity, acanthosis). Additionally, women with a history of gestational diabetes should be screened every 3 years at a minimum, and those with established prediabetes should have yearly screening. Finally, people with HIV

TABLE 1.1 Diagnostic Criteria for Prediabetes and Diabetes Mellitus

TEST	NORMAL RANGE	PREDIABETES RANGE	TYPE 2 DIABETES RANGE
Hemoglobin A1c	≤5.6%	5.7–6.4%	≥6.5%
Fasting glucose	≤99 mg/dL	100–125 mg/dL	≥126 mg/dL
OGTT (2-hour draw)	≤139 mg/dL	140–199 mg/dL	≥200 mg/dL
Random glucose with classic hyperglycemia symptoms or *a* hyperglycemic crisis	N/A	N/A	≥200 mg/dL

N/A, Not applicable; *OGTT,* oral glucose tolerance test.

should be screened yearly for diabetes given that this is an independent risk factor for cardiovascular disease. Additionally, certain HIV medications increase the risk of developing diabetes.

7. What tests should I use for diabetes/prediabetes screening?

Hemoglobin A1c (A1c) is the most widely used test for prediabetes and type 2 diabetes screening. It is available in most laboratories and is easy to complete, since fasting is not needed. Alternatively, a fasting glucose can be drawn. A 75-g oral glucose tolerance test (OGTT) is also a valid way to assess for prediabetes and type 2 diabetes and identifies a slightly different but overlapping group of people with glucose intolerance, but it is less convenient. The normal values for these tests are listed in Table 1.1. It is important to note that, in the absence of unequivocally high values and symptoms of hyperglycemia, or exam findings pathognomonic for insulin resistance, it is recommended that two different tests be obtained on the same blood sample or the same test at different times before making the diagnosis of diabetes.

In people who have a sibling or parent with type 1 diabetes, screening with autoantibodies can be offered. If two or more of these antibodies are positive (autoantibodies to insulin, glutamic acid decarboxylase [GAD65], islet antigen 2, or zinc transporter 8), referral to a diabetes center can be offered, and yearly monitoring for dysglycemia is recommended.

8. Can diabetes be prevented?

The Diabetes Prevention Program (DPP) demonstrated the significant beneficial effect of intensive lifestyle modifications in people with prediabetes to prevent progression to type 2 diabetes. Excellent randomized controlled trials have shown that individuals at high risk for developing type 2 diabetes who receive specific pharmacotherapy may experience reduced rates of progression to overt diabetes. However, the risks of these medications may outweigh the benefits in certain people. The American Diabetes Association (ADA) recommends pharmacotherapy (metformin) in people who are at high risk for progression to diabetes because of multiple risk factors at baseline, or in those who have a persistently elevated HbA1c of >6% despite lifestyle modifications.

The ADA specifically recommends active prevention in people at high risk for the development of type 2 diabetes. This includes intensive lifestyle changes (healthy caloric reduction and 150 minutes per week of moderate to vigorous aerobic exercise) with a goal of at least 7% body weight loss.

More recently, a monoclonal antibody, teplizumab, was approved to delay the onset of overt type 1 diabetes in people at risk of type 1 diabetes who are older than age 8 years. Teplizumab was shown to delay the onset of stage 3 type 1 diabetes by 25 months versus placebo. This medication should be administered under the care of a Diabetes Center of Excellence and requires monitoring for adverse events (especially leukopenia).

9. Why do people get diabetes?

Type 1 diabetes occurs due to the autoimmune destruction of the beta cells of the pancreas. Individuals with this form of diabetes often have family members with other autoimmune diseases. Type 2 diabetes has a strong genetic component but is influenced by environmental factors.

10. What are the different types of diabetes?

In the past, diabetes was classified as either type 1, type 2, gestational, or “secondary” diabetes. The most current classification of diabetes includes type 1, type 2, gestational diabetes, and

TABLE 1.2 Spectrum of DM Classified by A Status and β-Cell Function

	A+	A–
β+	A+/β+ Presence of autoantibodies but preserved β-cell function. (Stage 1–2 type 1 DM, ketosis-prone DM)	A–/β+ Absence of autoantibodies and preserved β-cell function. (Type 2 DM)
β-	A+/β– Presence of autoantibodies and absent β-cell function. (Stage 3 type 1 DM)	A–/β– Absence of autoantibodies with absent β-cell function. (Pancreatogenous DM)

A, Antibody; *DM*, diabetes mellitus.

TABLE 1.3 Stages of Type 1 Diabetes Development

STAGE	STAGE 1	STAGE 2	STAGE 3
Antibody positivity	≥2 antibodies	≥2 antibodies	≥2 antibodies
Other laboratory findings	Normal blood glucose	Fasting glucose 100–125 mg/dL 2-hour OGTT 140–199 mg/dL A1c 5.7–6.4%	Fasting glucose ≥126 mg/dL 2-hour OGTT ≥200 mg/dL A1c ≥6.5%
Symptoms	No symptoms	No symptoms	Classic diabetes symptoms (polyuria, polydipsia, weight loss, DKA)

DKA, Diabetic ketoacidosis; *OGTT*, oral glucose tolerance test.

"other" types, which include monogenic diabetes, pancreatic failure or damage (e.g., cystic fibrosis, pancreatitis, trauma, pancreatectomy), or drug-induced diabetes (including glucocorticoid-induced diabetes, HIV medication–related diabetes, immune checkpoint inhibitor–related diabetes, and organ transplant–related diabetes).

Another way to classify diabetes is to consider antibody status and beta cell function (Aβ±), which places all forms of diabetes along a spectrum. In this system, for example, type 1 diabetes would be reclassified as autoimmune positive and beta cell negative (A+/β-) to indicate that it is a disease of hyperglycemia in the presence of autoimmunity with no beta cell production of insulin. Similarly, one might think of patients with type 1 diabetes during the honeymoon period as A+/β+ (an autoimmune disorder of pancreas but with continued beta cell function) and type 2 diabetes as A-/β+ and post-pancreatectomy diabetes as A-/β- (see Table 1.2).

11. What is the natural history of type 1 diabetes?

The natural endpoint of type 1 diabetes is a lifelong requirement for insulin therapy. There is often a "honeymoon phase" soon after the diagnosis of type 1 diabetes, during which beta cells are still able to produce a small amount of insulin, and insulin requirements may be low. See Table 1.3 for a summary of the stages of type 1 diabetes, adapted from the ADA Standards of Care 2025. Notably, the new drug teplizumab is an immunotherapy approved for use in individuals with stage 2 type 1 diabetes to delay the progression to stage 3 type 1 diabetes.

12. What is the natural history of type 2 diabetes?

Individuals with type 2 diabetes generally start out with some degree of insulin resistance and develop insulin deficiency that worsens over time. Diabetes (with hyperglycemia) does not develop until the pancreatic beta cells are unable to adequately produce enough insulin to compensate for the individual's insulin resistance. Though noninsulin agents may initially be effective for restoring euglycemia, additional agents are often needed over time to maintain glycemic control. Lifestyle changes including increased physical activity and interventions leading to weight loss are effective strategies to reduce insulin resistance and usually allow people to reduce the number of medications needed to achieve and maintain goal A1c. Individuals with a shorter duration of diabetes may even be able to induce "remission" of diabetes and completely eliminate the need for medications for a period of time with significant and sustained lifestyle changes with or without medications leading to at least 15% weight loss. If individuals are on several noninsulin agents but have not achieved goal A1c, insulin is often added to the regimen. Some people with type 2 diabetes may require basal-bolus insulin therapy (as with type 1 diabetes mellitus to achieve glycemic control.

13. Who develops ketosis-prone diabetes?

This is a less commonly encountered form of diabetes characterized by a temporary lack of insulin production by the pancreatic beta cells. Ketosis-prone diabetes disproportionately affects non-White individuals. People present with diabetic ketoacidosis (DKA) and require insulin therapy to manage the DKA and for a short time after the resolution of DKA. However, most individuals can recover beta cell function and can be tapered off insulin therapy within a few months. In fact, people tend to become hypoglycemic within weeks of hospital discharge if maintained on their original basal-bolus regimen, unless blood glucose values are closely monitored, and the insulin regimen is reduced or eliminated. Once the immediate post-DKA period of glucose toxicity has resolved and beta cell function is regained, people can typically be maintained on noninsulin agent(s) for 10 years or more. Without sustained lifestyle modifications and medication adherence, individuals are at risk for repeated cycles of DKA, glucose toxicity, insulin use, possible hypoglycemia, and recovery.

14. What is LADA?

LADA stands for “latent autoimmune diabetes of adulthood.” This is now considered an outdated term. It is understood that type 1 diabetes is commonly diagnosed in adulthood and should be considered in any person newly diagnosed with diabetes, regardless of age.

15. What other causal factors should I be thinking about when I see a person with high glucose?

When evaluating a person with high blood glucose, a new diagnosis of diabetes or existing poorly controlled diabetes should always be at the forefront of consideration. However, there are other causes of hyperglycemia that ought to be considered. The most common nondiabetes cause is glucocorticoid administration. Though most individuals do not develop hyperglycemia while on glucocorticoids, glucocorticoids may precipitate hyperglycemia in those with underlying glucose intolerance. Critical illness and medical conditions such as infections may also cause hyperglycemia because of increased stress with cortisol, epinephrine, and inflammatory cytokine production. Similarly, people with hypercortisolism—either from ACTH secretion from a pituitary tumor, ectopic tumor, or from a cortisol-producing adrenal tumor—may develop hyperglycemia. Other rare causes of hyperglycemia include acromegaly from a growth hormone–secreting pituitary adenoma or a catecholamine-producing tumor such as pheochromocytoma or paraganglioma. In the inpatient setting, people with glucose intolerance receiving intravenous dextrose, either as maintenance fluids or with IV medications, may also develop hyperglycemia. Those receiving enteral nutrition or total parenteral nutrition are at particularly elevated risk for developing hyperglycemia when nutrition is delivered in this nonphysiologic manner.

16. What is pancreatogenic or pancreatogenous diabetes?

This is a form of diabetes that develops when pancreatic endocrine function is compromised, resulting in decreased insulin production. People who have had recurrent acute pancreatitis or chronic pancreatitis, sustained abdominal trauma such as from a motor vehicle accident, or have undergone partial pancreatectomy are the most likely to develop pancreatogenous diabetes. Individuals who have had a total/complete pancreatectomy lack both beta cells (which produce insulin) and alpha cells (which produce glucagon) and require insulin to survive but are at substantial risk for hypoglycemia and often need only low doses of insulin because of glucagon deficiency.

17. What is cystic fibrosis–related diabetes (CFRD)?

People with cystic fibrosis are at higher risk than the general population for developing diabetes. Up to 50% of adults with cystic fibrosis develop CFRD. The pathogenesis of CFRD is related to ciliary dysfunction and pancreatic destruction, as well as chronic inflammation and insulin resistance. Because of this combined pathology, as well as the loss of alpha cell function (glucagon secretion), concurrent severe respiratory illnesses, chronic steroid use, and malnutrition, CFRD is difficult to manage, and patients should be referred to a diabetologist. All people with cystic fibrosis should undergo yearly screening with an OGTT as the standard, starting at age 10 years. A1c has been shown to be less sensitive, and if used, a suggested cutoff for diagnosis is 5.5%. Because of the pancreatic destruction and beta cell loss in CFRD, all patients should be treated with insulin.

18. What is transplant-related diabetes?

Post-transplant diabetes (PTDM) is ideally diagnosed with OGTT after discontinuation of supraphysiologic doses of glucocorticoids, after resolution of any acute infection, and after the initial recovery period has passed for the organ transplant. This is because up to 90% of transplant recipients have transient hyperglycemia following an organ transplant, but only 20–30% go on to develop PTDM. To date, there are no large randomized studies evaluating treatment regimens for PTDM, and it is currently recommended to choose the antihyperglycemic that fits the patient's individual profile (such as sodium-glucose transporter 2 [SGLT2] inhibitors in patients with heart or renal disease).

19. What is immune checkpoint–related diabetes?

The onset of beta cell destruction and consequent diabetes occurs in approximately 1% of people treated with immune checkpoint inhibitors. These medications are typically used for different malignancies, and the development of diabetes is irreversible. The most common types of checkpoint inhibitors to cause diabetes are Programmed-Death 1 (PD1) and Programmed-Death Ligand 1 (PDL1) inhibitors. Unfortunately, the risk of diabetes is hard to predict, and the presence of a family history of type 1 diabetes or autoantibodies has not been useful in predicting outcomes. It is not recommended to stop the immunotherapy if diabetes develops, given that it is unlikely to reverse, but to continue the therapy and to start an insulin regimen.

20. What is monogenic diabetes?

Unlike type 1 and type 2 diabetes, which are often multifactorial in etiology, monogenic diabetes is caused by a single gene mutations causing pancreatic beta cell dysfunction or insulin signaling defects. Individuals are typically younger at the time of diagnosis, do not require insulin, and lack autoantibodies. Monogenic diabetes is often inherited in an autosomal dominant pattern, and it is common to have multiple generations of family members affected. Neonatal diabetes and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. Identifying the gene(s) affected is beneficial from a therapeutic standpoint, as the various forms of monogenic diabetes are treated differently. For example, MODY caused by a mutation in the hepatocyte nuclear factor-1 alpha is most effectively treated with sulfonylureas, while MODY caused by a defect in the glucokinase gene is best treated with changes in diet alone. More than 15 types of monogenic diabetes have been identified, and investigations are ongoing.

21. How can insulin resistance be assessed clinically?

Insulin resistance has a wide array of clinical manifestations, including acanthosis nigricans, skin tags, hirsutism, ovarian hyperandrogenism, and androgenic alopecia. Of these, acanthosis nigricans is the most recognized sign and is described as symmetrical, velvety, light brown to black thickened plaques and accentuated skin marks that appear on knuckles and in intertriginous areas. The pathophysiology is thought to be due to increased insulin growth factor-1 receptors in fibroblasts and keratinocytes, which both directly and indirectly stimulate their proliferation. Insulin resistance can be estimated in people without diabetes using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score. Measurements of insulin resistance, such as the hyperinsulinemic-euglycemic clamp and HOMA-IR, are used in the research setting but not in the clinical setting due to nonvalidated insulin assays and reference ranges.

22. What is the metabolic syndrome?

The metabolic syndrome requires at least three out of five of the following for diagnosis: hyperglycemia, hypertension, hypertriglyceridemia, low HDL, or increased abdominal circumference. When present, the metabolic syndrome is associated with a significantly increased risk of heart disease, stroke, and diabetes. Treatment of each aspect of the syndrome is imperative to decrease the risk for cardiovascular events and requires intensive lifestyle modification with diet, exercise, and weight loss. Often, medications are needed to treat each individual component of the metabolic syndrome.

KEY POINTS

- Diabetes is the result of relative or absolute insulin deficiency. In type 1 diabetes the beta cell is destroyed and therefore unable to produce insulin, whereas in type 2 diabetes the beta cell cannot produce enough insulin to overcome underlying insulin resistance.
- Diabetes is diagnosed via blood testing and requires abnormal results on two separate occasions or two abnormal tests on the same blood sample to confirm the diagnosis unless there is "unequivocal hyperglycemia."
- The diagnostic criteria include HbA1c ≥6.5%, fasting blood glucose ≥126 mg/dL, random blood glucose ≥200 mg/dL in addition to typical symptoms of diabetes, or plasma glucose ≥200 mg/dL 2-hour after receiving a 75 g glucose load during an OGTT.
- The most recent standards of care from the ADA suggest categorizing diabetes as type 1, type 2, gestational, and "other" (i.e., pancreatic diabetes or medication-induced diabetes). Diabetes can also be conceptualized as falling on a spectrum of autoimmunity and beta cell function (A+/β-).
- Patients with type 1 diabetes require insulin therapy lifelong, though there is often a short-lived initial "honeymoon phase," during which pancreatic beta cells are still able to produce a small amount of insulin. In comparison, the natural history of type 2 diabetes is insulin resistance that develops prior to beta cell dysfunction, during which patients can be managed with noninsulin agents, followed by progressive insulin deficiency. Half of the patients with type 2 diabetes in the United States are on insulin therapy with or without a noninsulin agent(s).
- When evaluating a patient with hyperglycemia, a new diagnosis of diabetes or preexisting diabetes should be at the forefront of consideration. However, glucocorticoids, critical illness, or medical therapies such as enteral or parenteral nutrition may cause hyperglycemia. Acromegaly, Cushing syndrome, and pheochromocytoma are rare causes of hyperglycemia and diabetes.

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CHAPTER 2

Diabetes Mellitus: Acute and Chronic Complications

Rebecca C. Rosenberg, Adnin Zaman, and Cecilia C. Low Wang

1. What are the acute complications of diabetes?

Diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar state (HHS), and hypoglycemia.

2. What are the symptoms of hyperglycemia?

People are often asymptomatic, but when hyperglycemia is severe, individuals may report the "3 P's"—polyuria, polydipsia, and polyphagia—along with blurry vision and fatigue. People may also note more frequent urinary tract or genitourinary infections and/or delayed healing of skin infections or ulcers. With insulin deficiency, people go into a catabolic state and experience weight loss. Some individuals report feeling agitated or confused, although this is not common.

3. What is DKA, and how common is it?

DKA stands for diabetic ketoacidosis. Three elements are required for the diagnosis: uncontrolled hyperglycemia (recently lowered from >250 mg/dL to >200 mg/dL) or any degree of glycemia in individuals with known diabetes, metabolic acidosis, and increased ketone concentration. It occurs more often in people with type 1 diabetes and is the first presentation of type 1 diabetes in about 25% of patients. DKA accounts for 206,000 hospital admissions in the United States each year. The incidence of DKA in adults varies depending on the population studied but is estimated to occur in 5–8% of adults with type 1 diabetes per year. The highest rates of DKA occur in children and in adults <45 years old. This group of younger adults also has a 27-fold higher rate of hospitalization for DKA compared to adults ≥65 years old. The T1D Exchange Clinic Network shows that young adults aged 18–25 years have the overall highest occurrence of DKA.

4. What is the mortality rate for DKA?

Before the discovery and use of insulin in 1921, the mortality rate in DKA was >90%. The mortality rate for DKA in the United States and European countries is currently <2% but is >10% in countries with limited resources for acute care. DKA is the leading cause of death in children and young adults with type 1 diabetes (approximately 50% of all deaths in individuals with diabetes <24 years old).

5. Do all patients who develop DKA have type 1 diabetes?

No; people with type 2 diabetes may also develop DKA if the relative insulin deficiency is severe enough, such as with severe stress or concurrent illness. People with ketosis-prone diabetes, which is described in Chapter 1, are diagnosed when they present with DKA.

6. What causes DKA?

The two key factors are insulin deficiency and elevated levels of counter-regulatory hormones (catecholamines, cortisol, glucagon, and growth hormone). These factors result in increased hepatic glucose output from both gluconeogenesis and glycogenolysis. In addition, there is reduced peripheral uptake of glucose in skeletal muscle. Increased breakdown of triglycerides produces free fatty acids which are then oxidized to ketone bodies (beta-hydroxybutyrate and acetoacetate) in the liver; this results in consumption of bicarbonate and results in metabolic acidosis.

7. What are the precipitating factors for DKA?

Infection, lack of insulin, new diagnosis of diabetes, myocardial infarction, alcohol use, pancreatitis, stroke, and insulin pump malfunction may all cause DKA. Risk factors include psychiatric disorders, eating disorders, substance abuse, and homelessness. In the United States, the most common precipitating factor is lack of adherence to insulin therapy. Elsewhere in the world, infection is the most common precipitating factor.

8. What are the symptoms and signs of DKA?

People often present acutely with nausea and vomiting, abdominal pain, polyuria, polydipsia, and fatigue, and may also report weight loss. They may have decreased mental status but present with coma less than 25% of the time. Signs may include decreased skin turgor, dry mucous membranes, tachycardia, and hypotension. Patients in severe DKA may have Kussmaul respirations (respiratory compensation for metabolic acidosis) with "fruity" breath due to acetone production.

9. How is DKA diagnosed?

Besides the clinical presentation described above, laboratory findings of ketonemia and anion gap metabolic acidosis are needed for the diagnosis. Ketonemia may be documented using serum beta-hydroxybutyrate and may be underestimated if ketones are measured using the nitroprusside method. A definitive determination of metabolic acidosis can only be made with simultaneous measurement of serum chemistries and a blood gas measurement (ideally arterial blood gas at diagnosis; however venous blood gas may be used to monitor therapy). The serum bicarbonate is decreased, pH is decreased, and $PaCO_2$ is decreased. The anion gap is calculated using the equation: sodium $[Na^+]$ – chloride $[Cl^-]$ – bicarbonate $[HCO_3^-]$. Serum glucose is usually over 200 mg/dL but may be lower than 200 mg/dL (termed "euglycemic DKA") in the following situations: pregnancy, starvation, alcohol use, insulin therapy, and use of sodium-glucose cotransporter-2 (SGLT2) inhibitors. The glucose threshold for diagnosis of DKA was recently lowered in a joint statement by the ADA and other societies.

10. What is euglycemic DKA and how is treatment different?

Euglycemic DKA occurs most often in people who are taking an SGLT2 inhibitor. The relative insulin deficiency driving ketosis continues to be the main pathophysiology; however, urinary loss of glucose results in a lower serum blood glucose (<200 mg/dL) in the presence of ketoacidosis. Other risk factors for euglycemic DKA include pregnancy, prolonged fasting, and alcohol use. The main difference in the treatment of euglycemic DKA is that concurrent dextrose infusion is started at the initiation of the insulin infusion. Otherwise, the treatment for euglycemic DKA is similar to that for hyperglycemic DKA, with insulin infusion and hydration as mainstays of therapy until the acidemia is corrected. If the patient is on an SGLT2 inhibitor, it is recommended that this be discontinued indefinitely.

11. What are the basic principles of DKA management?

These are (1) volume repletion, (2) correction of electrolyte abnormalities, (3) management of ketonemia and hyperglycemia, and (4) identification and treatment of the precipitating event(s). DKA often resolves within 10–18 hours. Patients must be monitored every 1–2 hours initially, then every 2–4 hours, with serial vital signs, physical examination to determine volume status and mental status, urine output, basic metabolic panel (for bicarbonate, potassium, anion gap), and venous blood gas (pH) to assess treatment. Changes in the rate of intravenous fluid administration and insulin dose are often needed.

12. Should ketones be followed in the management of DKA?

When point-of-care beta-hydroxybutyrate measurements are available, these can be used to diagnose ketosis and monitor therapy. Unfortunately, ketones measured using the nitroprusside method detect acetoacetate and acetone but not beta-hydroxybutyrate, which is the main ketone body produced in DKA. Serial measurement of ketones would therefore not be useful using the nitroprusside method.

13. When can patients be transitioned off the intravenous insulin infusion after treatment for DKA?

When the acidemia (determined by the absolute bicarbonate concentration) and ketosis have resolved, the patient is clinically improved (off pressors) and able to tolerate oral intake, and the precipitating cause(s) have been addressed. Factors that predict the successful transition of intravenous insulin to a subcutaneous regimen include a stable infusion rate of <3 units/hr with blood glucose <130 mg/dL.

TABLE 2.1 Diagnostic Criteria for DKA and HHS

MEASURE	EUGLYCEMIC DKA	HYPERGLYCEMIC DKA	HHS
Plasma glucose (mg/dL)	<200	≥200	≥600
Arterial pH	<7.30	<7.30	≥7.30
Beta-hydroxybutyrate (mmol/L)	≥3.0	≥3.0	<3
Serum bicarbonate (mEq/L)	≤18	≤18	≥18
Urine or serum ketones	Positive	Positive	Negative-small
Serum osmolality[a]	Variable	Variable	>300 mOs/kg

[a] Effective serum osmolality = 2[measured Na^+ (mEq/L)] + glucose (mg/dL)/18
Adapted from Kitabchi, et al., Fayfman, et al., and Umpierrez GE, et al..
DKA, diabetic ketoacidosis; *HHS,* hyperglycemic hyperosmolar syndrome.

14. What is HHS?

Hyperglycemic hyperosmolar syndrome.

15. Who presents with HHS?

HHS generally occurs in elderly patients with type 2 diabetes who have an impaired thirst mechanism or are unable to access free water for any reason.

16. What are the symptoms and signs of HHS?

People often report typical symptoms of hyperglycemia including polyuria, polydipsia, and blurred vision but also report weakness. They may have decreased mental status and often will have signs of dehydration including dry mucous membranes and decreased skin turgor. People with HHS may be hemodynamically unstable with decreased blood pressure.

17. Why do people with HHS generally not have ketoacidosis?

People with HHS have enough insulin production to suppress lipolysis and subsequent development of ketones. In addition, they may have lower circulating levels of counterregulatory hormones.

18. How does one distinguish between DKA and HHS? (Table 2.1)

People with DKA are more acidemic with ketonemia, while those with HHS have little to no ketones, normal serum bicarbonate, and total serum osmolality of >320 mOsm/kg or effective serum osmolality of >300 mOsm/kg. The latter often have more severe hyperglycemia (occasionally with blood glucose >1000 mg/dL) than those with DKA and have a more severe volume deficit.

19. Can a person have both DKA and HHS?

Yes, people may have features of both ketoacidosis and hyperosmolarity. People with HHS may have mild to moderate ketonemia and may have a concomitant metabolic acidosis due to lactic acidosis, uremia, or alcoholic ketoacidosis. Those with both DKA and HHS have a higher risk for mortality.

20. What is needed to diagnose HHS?

People with HHS have a total serum osmolality of >320 mOsm/kg or effective serum osmolality of >300 mOsm/kg, serum glucose of ≥600 mg/dL, and little to no ketones. Effective osmolality = sodium ion (mEq/L) × 2 + glucose (mg/dL)/18 + BUN (mg/dL)/2.8.

21. What is the key to treating HHS?

People with HHS are extremely volume depleted; the key to treatment is adequate volume repletion.

22. What role does insulin play in the treatment of HHS?

Insulin therapy is important but is secondary. Unlike the treatment of DKA, in which insulin deficiency is the most important driving factor, correction of volume loss is the critical element in the management of HHS.

23. Describe the signs and symptoms of hypoglycemia

Shakiness, diaphoresis, irritability, hunger, and fatigue. Neuroglycopenic symptoms include confusion, unusual behavior, visual disturbances, and loss of consciousness. People with severe hypoglycemia have a lowered threshold for seizures and may appear to be intoxicated, with slurred speech and clumsiness. Hypoglycemia can be fatal, with recent reports indicating that 4–10% of deaths in type 1 diabetes were caused by hypoglycemia.

24. What are the common reasons people with diabetes become hypoglycemic?

Mistimed insulin (such as administering meal insulin or a glucose-lowering agent without adequate oral intake), too much basal insulin, too much prandial and/or correctional insulin for an individual's needs, physical activity, renal insufficiency or failure with decreased renal contribution to gluconeogenesis and clearance of insulin. Other causes are similar to those in people with or without diabetes: liver failure, cardiac failure, sepsis, critical illness, untreated adrenal insufficiency, untreated hypothyroidism, and starvation or malnutrition. People with diabetes rarely have insulinomas but this is in the differential diagnosis for hypoglycemia.

25. What types of diabetes therapies are associated with hypoglycemia?

Sulfonylureas, glinides (repaglinide, nateglinide), and insulins.

26. What noninsulin diabetes therapies are associated with a low risk of hypoglycemia?

Metformin, acarbose, thiazolidinediones, dipeptidylpeptidase-4 inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists, SGLT2 inhibitors, and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP1 receptor agonists.

27. What factors increase the risk of hypoglycemia?

People with type 1 diabetes are two to three times more likely to become hypoglycemic. Iatrogenic hypoglycemia occurs more frequently when people have severe insulin deficiency, and the risk increases with increasing duration of diabetes. Other risk factors include advancing age, intensive glycemic control, renal disease, and decreased cognitive function.

28. What is "hypoglycemia unawareness"?

People with diabetes typically develop adrenergic symptoms, often associated with neuroglycopenia, when blood glucose levels drop below the normal glucose threshold. Hypoglycemia unawareness occurs when a person has had recurrent episodes of hypoglycemia, since repeated hypoglycemia downregulates beta-adrenergic receptors thus lowering the glucose level that causes hypoglycemic symptoms. Patients often need assistance from others to recognize and treat hypoglycemia. Hypoglycemia-associated autonomic failure consists of hypoglycemia unawareness and impaired counterregulatory hormone response.

29. Is hypoglycemia unawareness reversible?

Yes, with strict avoidance of hypoglycemia for a period of time (weeks to months), people regain hypoglycemia awareness.

30. How is hypoglycemia treated?

With 15 g of carbohydrates (glucose tablets or gel, half cup or 4 ounces of juice or regular soda, one cup or 8 ounces of milk, one tablespoon of honey, three three-packs of SweeTARTS, or approximately three rolls of Smarties). For severe hypoglycemia and/or when people are unable to take anything by mouth, glucagon should be used.

31. What should be done if a person is unconscious and severe hypoglycemia is suspected?

Call 911 and use glucagon. Newer formulations of glucagon include a nasal spray, autoinjector, and prefilled syringe, which are preferred over the older glucagon emergency kits.

32. What are key elements of education needed to prevent and avoid hypoglycemia?

Education is an important approach to decrease the risk of iatrogenic hypoglycemia. Key elements of education include recognizing the symptoms of hypoglycemia, proper treatment of hypoglycemia, and being familiar with situations in which one might anticipate a higher risk for hypoglycemia. These elements need to be reviewed at every visit. In addition, people may require guidance on dietary and exercise modifications, medication adjustments, and sensible glucose monitoring methods. Meticulous surveillance by the provider is imperative.

33. What are common long-term complications of diabetes mellitus?

Long-term complications of diabetes are often divided into microvascular and macrovascular; the former include neuropathy, retinopathy, and diabetic kidney disease, while the latter includes atherosclerotic cardiovascular disease (coronary heart disease, cerebrovascular disease, and peripheral arterial disease presumed to be of atherosclerotic origin). Macrovascular disease is the leading cause of morbidity and mortality for individuals with diabetes and the largest contributor to the direct and indirect costs of diabetes, but microvascular disease causes significant morbidity and decreased quality of life. Diabetic foot ulcers are multifactorial and cannot be classified neatly into a "micro- versus macrovascular" complication.

Diabetes is associated with a number of comorbid conditions including obesity, obstructive sleep apnea, fatty liver disease, fractures, pancreatitis, hearing loss, certain cancers (liver, pancreas, endometrium, colon/rectum, breast, and bladder), depression, anxiety, cognitive impairment and dementia, eating disorders, and periodontal disease, which will not be discussed in this section.

34. Why do individuals with diabetes develop these complications?

The basic mechanisms underlying the development of micro- and macrovascular complications are complex and under intensive investigation by researchers around the world. Uncontrolled hyperglycemia, hyperinsulinemia, insulin resistance, and associated conditions including disordered lipid metabolism, hypertension, and obesity conspire to create a "perfect storm" leading to increased oxidative stress and inflammation resulting in the development of these complications. With microvascular complications, hyperglycemia leads to activation of protein kinase C and reactive oxygen species and generation of toxic products of increased glucose metabolism (such as advanced glycation end-products, methylglyoxal).

35. What fundamental factors need to be managed to prevent microvascular complications?

Hyperglycemia, hypertension, and dyslipidemia are all important comorbidities that must be managed to prevent diabetic complications. Importantly, glycemic control to an A1c <7% is the strongest recommendation from the ADA to prevent microvascular complications of diabetes. Both the Diabetes Control and Complications Trial (DCCT) and the DCCT-EDIC (long-term follow-up study) for type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS) and its follow-up study for type 2 diabetes, provide strong evidence for this recommendation.

36. How common is diabetic retinopathy?

Diabetic retinopathy is the most common microvascular complication of diabetes. Globally, diabetic retinopathy affects almost 100 million people. It is the most common cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma and cataracts occur earlier and at a higher frequency in people with diabetes.

37. How does diabetic retinopathy manifest?

People are asymptomatic in the early stages, which can only be diagnosed with routine ophthalmologic screening. The different types include nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and diabetic macular edema (DME). NPDR is the early stage and includes a number of retinal findings including microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, and venous caliber changes. The more advanced stage of PDR is characterized by preretinal neovascularization. Evolving technologies are allowing for the detection of more subtle abnormalities such as deficits in retinal function and the neural layer. DME can occur at any stage of diabetic retinopathy and is the most common cause of visual loss in diabetic retinopathy. In DME, the blood–retina barrier breaks down with leakage of circulating fluid and proteins into the neural retina leading to abnormal retinal thickening and cystoid edema of the macula.

38. How is diabetic retinopathy managed?

The mainstay of managing all diabetic complications is to strive for optimal glycemic control (A1c <7.0% without hypoglycemia). Specific treatment options for retinopathy include focal and panretinal laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factor, intravitreal steroids, and vitreoretinal surgery. The eye-specific therapeutic paradigm is to treat advanced disease (PDR and/or DME). Rapid reductions in A1c should be avoided if an individual has NPDR or PDR because this can precipitate marked worsening of retinopathy; instead, more gradual improvements in glycemic control are recommended.

39. How common is diabetic kidney disease (DKD)?

DKD occurs in approximately 20–40% of individuals with diabetes. It may already be present at diagnosis of type 2 diabetes but usually develops only after 10 years of type 1 diabetes. One study of more than 159,000 adults with newly diagnosed type 2 diabetes in the United Kingdom found that 20.7% had nephropathy at the time of diagnosis. DKD disproportionately affects middle-aged Blacks, Native Americans, and Hispanics, who continue to have higher rates of end-stage renal disease (ESRD).

40. Is there more than one manifestation of DKD?

Yes—albuminuria (urinary albumin excretion), decreased glomerular filtration rate, glomerular hematuria, other abnormalities of the urinary sediment, or abnormalities on imaging studies are all manifestations of DKD. Not all individuals with DKD and reduced eGFR have increased albuminuria. The UKPDS showed that only about half of people who developed an estimated creatinine clearance of <60 mL/min/1.73 m^2 ever tested positive for albuminuria.

41. What treatments are effective in preventing the progression of DKD to ESRD?

Good glycemic control (A1C <7.0% without hypoglycemia), good blood pressure control, and avoidance of dehydration and nephrotoxic drugs are all critical elements. Significant efficacy in preventing kidney disease progression has been demonstrated for the renin-angiotensin-aldosterone system inhibitors, specifically the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, the SGLT2 inhibitors and the nonsteroidal mineralocorticoid receptor antagonist, Finerenone. Although it has been a secondary outcome in the clinical trials, the long-acting Glucagon like GLP1 receptor agonists have also shown efficacy. Of note, combined therapy with ACE inhibitors and ARBs is not recommended, since the combination has been shown to be harmful in the ONTARGET and VA NEPHRON-D trials.

42. What types of diabetic neuropathies are there?

Distal symmetric sensorimotor polyneuropathy (the most common), autonomic neuropathy, focal limb neuropathies, mononeuropathies, entrapment syndromes such as carpal tunnel syndrome, diabetic amyotrophy (proximal motor neuropathy), diabetic truncal radiculopathy, and acute sensory neuropathy. The diabetic neuropathies have two distinct patterns of progression: sensory and autonomic neuropathies generally progress gradually with increasing duration of diabetes, while mononeuropathies, radiculopathies, and acute painful neuropathies may be quite severe but are short-lived and resolve completely. The diabetic neuropathies encompass heterogeneous clinical presentations, and the incidence, prevalence, and natural history of diabetic neuropathies are not well defined. This is due to variable diagnostic criteria, lack of standardized methods for evaluation, and lack of recognition by clinicians.

43. What is the pathogenesis of diabetic neuropathies?

Both metabolic abnormalities within the nerve and/or Schwann cell, as well as microvascular injury, contribute to diabetic neuropathy. In distal symmetric polyneuropathy, progressive axonal degeneration occurs in different fiber types and is accompanied by demyelination.

44. What are the symptoms of distal symmetric polyneuropathy and what is the usual pattern of progression?

Numbness, the feeling of a toe or part of the foot "falling asleep," prickling or tingling, stabbing, or burning, electrical shocks, or aching pain. Symptoms start in the toes or plantar surface of the feet in a symmetric pattern, and travel proximally. Patients do not develop symptoms in the upper extremities until lower extremity symptoms have reached the knees ("stocking-glove distribution"). Distal symmetric polyneuropathy is a diagnosis of exclusion; other causes must be considered including chronic inflammatory demyelinating polyneuropathy, vitamin B_{12} deficiency (particularly in those on metformin for longer than a year), hypothyroidism, and uremia.

45. How is diabetic neuropathy treated?

Tight glycemic control prevents the progression of neuropathy but does not reduce pain in distal symmetric polyneuropathy. FDA-approved therapies for painful diabetic neuropathy are pregabalin and duloxetine, which are also recommended by the American Diabetes Association as first-line therapies. Other therapies include gabapentin, sodium valproate, venlafaxine, amitriptyline, dextromethorphan, topical capsaicin, lidocaine patches, isosorbide dinitrate spray, and opioids. Nonpharmacologic therapies such as percutaneous electrical nerve stimulation can also be tried but lack data to support their use. Therapies target symptoms and not the underlying mechanisms.

46. What are foot problems people with diabetes can experience?

Diabetic foot ulcers, insensate feet, diabetic foot infection, foot deformity including Charcot foot, peripheral artery disease, and amputations.

47. What are the important strategies for preventing diabetic foot ulcers?

People should be aware of the risk factors for diabetic foot ulcers and amputation, including poor glycemic control, peripheral neuropathy with loss of protective sensation, cigarette smoking, foot deformity, preulcerative callous or corn, peripheral artery disease, history of a foot ulcer, prior amputation, visual impairment, and DKD (particularly ESRD on dialysis). Proper foot care includes assessment of skin and nails, palpation or visual surveillance (including use of an unbreakable mirror if needed) to monitor the condition of the feet, use of well-fitting shoes (custom-fitted in select circumstances), and proper wound care if an ulcer develops.

48. What are the manifestations of diabetic autonomic neuropathy?

These include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

49. What are the components of cardiac autonomic neuropathy?

Early cardiac autonomic neuropathy is usually asymptomatic and only manifests as decreased heart rate variability with deep breathing or the Valsalva maneuver. Later, it manifests as resting tachycardia and orthostatic hypotension. Cardiac autonomic neuropathy is independently associated with mortality.

50. When do people with diabetes develop gastroparesis and when should it be suspected?

People with type 1 diabetes generally do not develop gastroparesis until 10–15 years after diabetes is diagnosed, whereas those with type 2 diabetes often do not develop gastroparesis until after a longer duration of diabetes. Gastrointestinal neuropathies can manifest along any portion of the gastrointestinal tract and include esophageal dysmotility, gastroparesis, diarrhea with or without fecal incontinence, and constipation. Patients who have difficult-to-control blood glucose (especially in a pattern of postprandial hypoglycemia followed by prolonged hyperglycemia) and unexplained gastric or esophageal symptoms should be suspected of having gastroparesis.

51. How is gastroparesis diagnosed?

After the exclusion of mechanical obstruction and gastric or peptic ulcer, the gold standard for diagnosis is gastric-emptying scintigraphy. People must discontinue any drugs that might affect gastric emptying, fast overnight, then consume a standard low-fat radiolabeled meal within 10 minutes. Imaging is performed at baseline, 1, 2, and 4 hours in a standing position. Glucose values should be <275 mg/dL. Delayed gastric emptying is defined as >60% retention at 2 hours or >10% retention at 4 hours. Limitations include lower sensitivity for detecting mild or moderate gastroparesis, potential overdiagnosis in women who have a physiologic delay of approximately 15%, intraindividual variation of up to 24%, and the use of a low-fat, low-fiber test meal to standardize testing conditions but which may not be similar to actual meals that they consume, leading to under-diagnosis of gastroparesis. Alternatives include a gastric emptying breath test using a radiolabeled carbon-containing test meal (carbon13–labeled *Spirulina platensis* or octanoic acid) or a wireless motility capsule (a "SmartPill"). For the breath test, radiolabeled carbon is released during digestion, and the carbon dioxide released through ventilation is measured 4–6 hours later.

Comparative studies suggest that the breath test may be as accurate as scintigraphy, but evidence supporting the use of the wireless motility capsule is of low quality.

52. What is diabetes-related distress?

This term refers to the negative emotional or affective state resulting from the challenges of living with the many demands of diabetes. It may be defined as "decreased quality of life due to a combination of the medical and psychological burden of diabetes as a complex and chronic condition creating emotional distress often hidden from providers and sometimes from the sufferer." Diabetes-related distress can negatively impact diabetes management and outcomes. The level of diabetes distress does not appear to be associated with the duration of diabetes but has been noted to be much higher in younger patients, and in female, non-White patients, those with higher BMI, and those treated with insulin as compared to non-insulin-treated patients. It is distinct from depression or overall emotional well-being.

53. How common is depression in diabetes?

Depression is two to three times more common in people with diabetes than in the general population. There is now evidence emerging that depression may be a risk factor for developing diabetes (up to 60% risk). Conversely, the pooled relative risk for developing depression in individuals with preexisting diabetes is 1.15.

54. How can macrovascular disease be prevented in diabetes?

Standard measures include tobacco cessation and lowering of blood pressure and LDL cholesterol. The intensity of LDL lowering is greater for individuals with diabetes as compared with individuals of low to moderate risk without diabetes. Regular physical activity and a healthy dietary pattern that emphasizes intake of fruits, vegetables, reduced saturated fat, and low-fat dairy products, such as the Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) diet is recommended.

KEY POINTS

Acute Complications

- The basic principles of DKA management are (1) volume repletion, (2) correction of electrolyte abnormalities, (3) management of ketonemia and hyperglycemia, and (4) identification and treatment of the precipitating event(s).
- Patients may be transitioned off the intravenous insulin infusion after resolution of DKA when the following criteria are met: acidemia and ketosis have resolved, the patient is clinically improved and able to tolerate oral intake, and the precipitating cause(s) have been addressed.
- Patients with DKA are more acidemic with ketonemia, while those with HHS have little to no ketones, normal serum bicarbonate, and elevated serum osmolality.
- Patients with HHS often have more severe hyperglycemia (occasionally with blood glucose >1000 mg/dL) than those with DKA and have a more severe volume deficit.

Chronic Complications

- Hypoglycemia unawareness occurs when a person has had recurrent hypoglycemia leading to downregulation of beta-adrenergic receptors and a lower glucose level at which individuals develop hypoglycemic symptoms. Hypoglycemia unawareness is reversible with strict avoidance of hypoglycemia for a period of time (weeks to

Continued

KEY POINTS—cont'd

months). Hypoglycemia-associated autonomic failure consists of hypoglycemia unawareness and impaired counterregulatory hormone response.

- Diabetes-related kidney disease may manifest in various ways. These include albuminuria (urinary albumin excretion), decreased glomerular filtration rate, glomerular hematuria, other abnormalities of the urinary sediment, or abnormalities on imaging studies. Not all individuals with diabetes-related kidney disease and reduced eGFR have increased albuminuria. Initiation of a SGLT2 inhibitor is indicated and a specific mineralocorticoid antagonist should be considered.
- The diabetic neuropathies have two distinct patterns of progression. Sensory and autonomic neuropathies generally progress gradually with increasing duration of diabetes. In comparison, mononeuropathies, radiculopathies, and acute painful neuropathies present acutely, are short lived, and resolve completely.
- The best strategy for both primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in diabetes includes tobacco cessation, regular physical activity, and a heart-healthy diet, with weight loss, if needed. In addition, people should receive a statin and maintain good blood pressure control. For high-risk individuals or those with established ASCVD, the use of a glucose-lowering agent indicated for the reduction of cardiovascular disease risk in diabetes is strongly recommended. For those with established ASCVD, aspirin is recommended, and rivaroxaban and icosapent ethyl should be considered.

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CHAPTER 3

Type 1 Diabetes Mellitus

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1. How is type 1 diabetes diagnosed and differentiated from type 2 diabetes?

Diabetes is diagnosed based on glycosylated hemoglobin (A1C), fasting plasma glucose value, or 2-hour plasma glucose value after a 2-hour oral glucose tolerance test (OGTT). The diagnosis can also be made with an elevated random glucose value in addition to symptoms of hyperglycemia (Table 3.1). Once the glucose-based diagnostic criteria have been met, identifying whether the person with newly diagnosed diabetes has type 1 diabetes requires further investigation. Autoimmune type 1 diabetes is caused by the destruction of the insulin-producing beta cells in the pancreas by the immune system. Damage can begin months to years before the onset of symptoms, and eventually leads to an absolute deficiency of insulin. Autoimmune type 1 diabetes occurs in stages. Stage 1 is when the patient is presymptomatic and has normal glucose levels but has autoantibodies. Stage 2 is when the patient progresses to some dysglycemia but is still asymptomatic. Stage 3 is when the patient progresses to hyperglycemia and is typically symptomatic. Most patients are not diagnosed until they reach stage 3 and up to 60% of patients are diagnosed following an episode of diabetic ketoacidosis (DKA). The diagnosis of type 1 diabetes is based on hyperglycemia, hyperglycemic symptoms (polyuria, polydipsia, and blurred vision), the presence of autoantibodies (GAD Ab, IA2 Ab, ZNT8 Ab, Insulin Ab – if not previously on insulin therapy), and the absence of insulin (C-peptide <1). When distinguishing between type 1 and type 2 diabetes, younger age, lean body mass, and rapid onset of symptoms are characteristics more commonly associated with type 1 diabetes. However, type 1 diabetes can be diagnosed at any age. It is important to note that the classification of diabetes is not always straightforward. Misclassification of type 1 diabetes in adults is common; over 40% of those developing type 1 diabetes after age 30 are initially classified as having type 2 diabetes. Adults with suspected type 1 diabetes should be tested for islet autoantibodies. Glutamic acid decarboxylase (GAD) should be tested first. If negative, islet tyrosine phosphatase 2 (IA2) and zinc transporter 8 (ZNT8) should be ordered. The presence of an islet antibody is predictive of type 1 diabetes. C-peptide measurement, which indicates the amount of insulin the body is producing, can also be useful, as low or absent C-peptide levels can confirm the diagnosis of type 1 diabetes. Other, more rare forms of diabetes should not be forgotten.

2. Can type 1 diabetes be prevented?

Currently, there is no known way to prevent type 1 diabetes. The exact cause is not fully understood, but it is believed to involve a combination of genetic and environmental factors. Research is ongoing to understand the triggers and mechanisms behind the development of type 1 diabetes, with the hope that this could eventually lead to preventive measures. Some areas being investigated include genetic screening to identify individuals at high risk based on their genetic profile, identification of potential environmental triggers that might initiate the autoimmune response, and immune-modulating therapies that could prevent or delay the progression of the autoimmune response. Teplizumab, an anti-CD3 monoclonal antibody targeting the autoimmune-mediated destruction of beta cells, is the first medication approved by the US Food and Drug Administration (FDA) to delay the progression of type 1 diabetes. Teplizumab is indicated in adults and pediatric patients aged 8 years and older with stage 2 type 1 diabetes and is administered via intravenous infusion over a 14-day period in a clinical setting. Since type 1 diabetes is typically not diagnosed until a person has reached stage 3, screening appropriate individuals to identify those with earlier stages that may benefit from teplizumab is critical.

3. What is the general approach to the treatment of type 1 diabetes?

The mainstay of treatment of type 1 diabetes is insulin, administered in a way that mimics normal physiologic insulin secretion. The goals of therapy are to prevent or delay the onset of long-term

TABLE 3.1 Criteria for the Diagnosis of Diabetes

1. A1C ≥6.5% (0.065; 48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the Diabetes Control and Complications Trial assay[a]
2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hour.[a]
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L).

[a] In the absence of unequivocal hyperglycemia, a diagnosis requires two abnormal test results from the same sample or in two separate test samples.

complications of diabetes, including retinopathy, kidney disease, neuropathy, and cardiovascular disease; to prevent treatment-induced hypoglycemia, and to maintain quality of life. For most individuals, the target of A1C is <7%, but this goal should be individualized on the basis of patient-specific factors. A fasting plasma glucose (FPG) target of 80–130 mg/dL and a postprandial glucose (PPG) target of <180 mg/dL correlate with a target A1C <7%. The American Diabetes Association (ADA) recommends a PPG target of <180 mg/dL, whereas the American Association of Clinical Endocrinologists (AACE) recommends a PPG target of <140 mg/dL. Coinciding targets for those using continuous glucose monitors include time in range (70–180 mg/dL) >70%, time above range (>180 mg/dL) <25%, time below range (<70 mg/dL) <4%, time <54 mg/dL <1%, and glycemic variability (% coefficient of variation) ≤36%.

Achieving good glycemic control in type 1 diabetes usually requires intensive insulin therapy (IIT). IIT is the use of multiple daily injections (MDIs) of insulin (both long-acting and rapid-acting formulations) or an insulin pump (with or without integration with a continuous glucose monitor) in an effort to mimic the normal insulin secretion pattern by the pancreas. IIT may also be referred to as *physiologic, multiple-component,* or *basal-bolus insulin therapy.* IIT is only one aspect of comprehensive, intensive diabetes therapy to achieve tight glycemic control. IIT is complex because it requires multiple injections or pump boluses each day in addition to basal insulin delivery, routine monitoring, and collaborative decision-making. The most successful IIT is delivered and adjusted on the basis of changes in nutritional intake, glucose levels, stresses, and physical activity. Automated insulin delivery (AID) systems that use continuous glucose monitoring data to automatically adjust insulin delivery via an insulin pump in real time provide even more intensive therapy and are discussed in more detail in question 17.

4. List the critical components of intensive insulin therapy.

- Frequent blood glucose monitoring (BGM) or continuous glucose monitoring (CGM)
- Defined and individualized target blood glucose (BG) levels
- Use of BGM or CGM data and glucose patterns to meet treatment goals
- Dose modifications according to the individual's response to the therapy
- Understanding of diet composition, specifically the carbohydrate content
- Careful balance of food intake, activity, and insulin dosage
- Use of accurate insulin-to-carbohydrate (I:C) ratios according to food intake
- Use of correction factors (CFs) for the adjustment of insulin according to glucose levels
- Patient education, motivation, and ongoing interaction between the patient and healthcare team

5. Summarize the studies evaluating optimal glycemic control to decrease chronic diabetes complications in type 1 diabetes.

The Diabetes Control and Complications Trial (DCCT), evaluating patients with recent-onset type 1 diabetes, showed that improved glycemic control (A1C <7%) with IIT significantly reduced the rates of microvascular complications, including progression of retinopathy, nephropathy, and neuropathy. The Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study demonstrated that these benefits persisted beyond the end of the initial DCCT trial despite equivalent glucose levels in the two groups in the posttrial period. In addition, the long-term follow-up study found that reductions in cardiovascular disease and mortality emerged over time in the intensive treatment arm. There was, however, a two- to three-fold increased risk of hypoglycemia with intensive treatment. The DCCT, published in 1993, still remains the basis of evidence for glycemic control in type 1 diabetes, but with advances in insulin therapies and technologies, the goal should be to achieve glucose levels in the target range while minimizing hypoglycemia and treatment burden. Newer studies are evaluating the relationship between time in range and long-term outcomes.

6. Which patients are candidates for IIT?

All people with type 1 diabetes should be considered potential candidates for IIT. However, the degree of intensification must be based on each person's individual situation and abilities. Patient characteristics that predict greater success with IIT include motivation, willingness to perform frequent BGM and record results or use a continuous glucose monitor, time available to spend with a diabetes educator, the ability to recognize and treat hypoglycemia, an understanding of how to manage sick days, and the presence of a supportive network of family or friends. In addition, the implementation of IIT requires a cohesive diabetes team that is available for frequent interaction and discussion about results from monitoring, insulin adjustments, and other issues.

7. What are the risks of IIT?

Hypoglycemia and weight gain are the most common adverse effects of insulin therapy. IIT in the DCCT resulted in a threefold increased risk of severe hypoglycemia compared with conventional treatment (62 episodes per 100 patient-years of therapy). Since the completion of the DCCT, newer rapid-acting and long-acting insulin analogs have been developed and are associated with less hypoglycemia compared with the short-acting and intermediate-acting human insulin products used in the DCCT. Frequent episodes of hypoglycemia can lead to loss of clinical warning symptoms (e.g., palpitations, sweating, hunger) with hypoglycemia (known as *hypoglycemia unawareness*). A unique risk of insulin pump therapy is DKA, as pump malfunctions or infusion site problems can interrupt insulin delivery. Finally, IIT requires time and commitment from the patient and may have negative psychosocial and economic implications.

8. What is the difference between basal insulin coverage and bolus insulin coverage?

IIT is designed to mimic the normal insulin secretion pattern, which includes continuous basal coverage in addition to bursts of insulin to regulate the rise in glucose after food intake (Fig. 3.1). Basal insulin secretion suppresses hepatic glucose production to control blood glucose levels in the fasting state and premeal periods. Normal basal insulin secretion from the pancreas varies slightly throughout the day, responding to changes in activity, blood glucose levels, and regulatory hormones. Basal insulin coverage in IIT is usually accomplished with injections of long-acting insulin analogs or with the basal infusion function on the insulin pump. Bolus insulin doses consist of

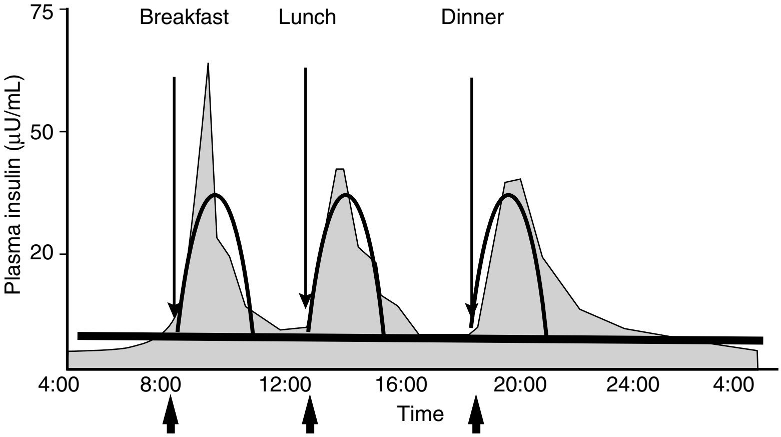

Fig. 3.1 Intensive insulin therapy pattern with MDIs.

two components, the *nutritional dose,* which is the amount of insulin required to manage glucose excursions after meals, and the *correction dose,* which is the amount of insulin required to reduce a high glucose level detected before a meal. Bolus coverage is accomplished by the administration of rapid-acting or short-acting insulin preparations or by using the bolus function on the insulin pump. Physiologic insulin secretion requirements are approximately 50% basal and 50% bolus.

9. How are basal and bolus insulins used with an MDI regimen?

A long-acting insulin is injected either once or twice daily to provide the basal insulin portion of an MDI regimen, which is approximately 50% of a patient's total daily dose. Ideally, basal insulin should cover background insulin needs only, independent of food intake. A rapid-acting or short-acting insulin is injected before meals to provide the bolus insulin portion of an MDI regimen (see Fig. 3.1). Rapid-acting insulin is preferred because of the rapid onset and short duration of action. A patient can adjust each bolus dose to match the carbohydrate intake and to correct for high glucose levels before the meal, whereas the basal dose remains constant from day to day. Premixed "biphasic" insulin preparations combine either a rapid-acting insulin analog or regular human insulin with a crystalline protaminated form of the analog or regular human insulin in an attempt to imitate basal or bolus therapy with fewer injections.

10. What are the currently available bolus insulin preparations?

Bolus insulin options include rapid-acting analogs (aspart, glulisine, and lispro), short-acting regular human insulin, and ultrarapid-acting agents (faster-acting insulin aspart, insulin lispro-aabc, and inhaled insulin). See Table 3.1 for a complete list of products and their pharmacodynamic profiles. All bolus insulin agents are effective at lowering PPG levels and A1C. Rapid-acting agents have a faster onset of action and shorter duration of action compared with short-acting insulin. Because of this, current guidelines recommend the use of rapid-acting agents over short-acting agents in patients with type 1 diabetes to reduce the risk of hypoglycemia; however, cost may necessitate the use of regular insulin in some patients. Ultrarapid-acting agents may be an option for patients who have rapid rises in glucose after meals and desire a bolus insulin with a faster pharmacokinetic onset. The ultrarapid-acting agents contain additives such as niacinamide, treprostinil, or citrate that enhance absorption and accelerate the onset of action.

11. What are the currently available basal insulin preparations?

Basal insulin options include long-acting analogues (glargine U-100, glargine U-300, degludec) and neutral protamine Hagedorn (NPH) insulin. See Table 3.1 for a complete list of products and their pharmacodynamics profiles. Insulin detemir was a commonly used basal insulin for years but was discontinued by the manufacturer in 2024. All basal insulin agents are effective at lowering FPG levels and A1C. The pharmacodynamics of NPH insulin make it a less ideal basal insulin because it has a distinct peak effect and does not last a full 24 hours. It must be administered twice daily in people with type 1 diabetes. Insulin glargine U-100 has an improved pharmacodynamic profile compared with NPH but may still exhibit a peak effect and may not last a full 24 hours in all people. Insulin glargine U-300 and insulin degludec are newer basal insulins without peak effects and have durations of action that exceed 24 hours. These pharmacodynamic benefits are appealing because they permit once-daily dosing without the effect wearing off, allow for more dosing flexibility, and are less likely to cause hypoglycemia. Studies have shown that these agents result in similar reductions in FPG and A1C but result in less nocturnal hypoglycemia compared with insulin glargine U-100.

12. When should bolus insulin be taken?

- Rapid-acting insulin should be taken 5–10 minutes before meals and snacks.
- Rapid-acting insulin can be taken:
  - 15–30 minutes before meals if the premeal BG is higher than 130 mg/dL
  - Immediately after eating, if gastroparesis or a concurrent illness is present
  - Upon arrival of food if unfamiliar with meal size, content, or timing (i.e., in a restaurant or hospital)
- Fast-acting insulin aspart (Fiasp) and insulin lispro-aabc (Lyumjev) should be taken at the beginning of the meal or within 20 minutes after starting the meal.
- Inhaled insulin should be taken at the beginning of the meal.
- Human regular insulin should be taken 15–30 minutes before meals.

13. When should basal insulin be taken?

- Insulin glargine U-100, glargine U-300, and degludec should be taken once a day at the same time each day.
- Insulin glargine U-100 may be taken at bedtime if the "dawn phenomenon" is present.
- Basal insulin analogs (glargine or degludec) cannot be mixed with other insulins.
- If nocturnal hypoglycemia results from taking a full dose of glargine at bedtime, an option would be to split the dose so that 50% is taken in the morning and the other 50% is taken in the evening, approximately 12 hours apart.
- NPH insulin is taken in the morning and at bedtime to avoid nocturnal hypoglycemia.
- Doses of insulin glargine U-300 and insulin degludec should not be adjusted more frequently than every 3–4 days because of their longer half-lives.

14. What is the role of BGM?

Optimal diabetes control requires frequent BGM (or CGM) to permit well-informed adjustments in insulin doses. Patients on IIT, who do not use CGM, should perform BGM at least four times daily, before meals, and at bedtime. Patients should also test if symptoms of hypoglycemia occur and should always test before driving if frequent hypoglycemia or hypoglycemia unawareness is present. BGM is crucial during times of intercurrent illness or stresses for early detection and potential prevention of hyperglycemic emergencies, such as DKA. Patients may also benefit from occasional testing 1–2 hours after meals. Patients using CGM may perform BGM with less frequent use of the glucometer, but the glucometer should still be easily accessible in case of emergencies or device failure. The role of CGM is described below. Also see Chapter 5 (Diabetes Technology).

15. What is an insulin pump?

An insulin pump is a small, lightweight, portable, battery-operated device, which is either attached directly to the body (patch pump) or worn on clothing or a belt similar to a pager (traditional pump). A traditional pump is composed of a pump reservoir (which holds a 2- to 3-day supply of rapid-acting or short-acting insulin), connected to an infusion set, which ends in a cannula that is inserted into the skin and changed every 2 to 3 days. A patch pump is tubing-free and consists of a disposable reservoir that attaches directly to the body with self-adhesive backing and a built-in infusion set in the device for insertion into the subcutaneous tissue. The patch pump is controlled by a handheld personal digital assistant (PDA). Insulin is delivered through either system in microliter amounts continuously over 24 hours. The user is responsible for setting the basal rates and determining the bolus doses, depending on the meal ingested and the results of BGM. Currently, four companies offer insulin pumps in the United States. Each pump has special features and functions that are unique and help with the flexibility of pump use. To learn more about insulin pumps, contact the companies listed in Table 3.2. Also see Chapter 5 (Diabetes Technology).

16. What is CGM?

Currently, four companies offer CGM devices in the United States. To learn more about CGM products, contact the companies listed in Table 3.3. CGM devices report interstitial glucose levels in real time and provide an insight into glucose trends. Traditional systems consist of a sensor, which is placed just under the skin and senses the glucose level in interstitial fluid; a transmitter, which is attached to the sensor and transmits the glucose data; and a separate receiver, which collects the data from the transmitter and displays current and stored glucose readings. The receiver updates the user's glucose levels in real time and displays glucose trends with a graph and arrows. With some CGM devices, a smartphone or an insulin pump can be used as the receiver. Most CGM devices have received approval from the FDA for the data to be used for treatment decision-making without verification by BGM. Some CGM devices require routine calibration with BGM to maintain accuracy; some systems do not. Traditional CGM devices also provide alerts to the patient when glucose levels are too high or too low or are falling or rising rapidly. A continuous or "real-time" CGM communicates readings continuously from the transmitter to the receiver, while an intermittent or "flash" CGM system only communicates readings on demand after scanning the receiver over the transmitter. CGM use with IIT can reduce A1C,

TABLE 3.2 Pharmacodynamics of Insulin Preparations

PREPARATIONS (U-100 UNLESS OTHERWISE NOTED)	ONSET	PEAK[A]	DURATION[A]
Bolus Insulin Products			
Ultra-rapid acting			
Insulin aspart (Fiasp)	15–20 min.[b]	90–120 min.	5–7 hours
Insulin lispro-aabc (Lyumjev)	15–17 min.[c]	120–174 min.	4.6–7.3 hours
Insulin human—inhaled (Afrezza)	12 min.	35–40 min.	90–180 min.
Rapid-acting Insulin Analogs			
Insulin aspart (NovoLog)	10–20 min.	30–90 min.	3–5 hours
Insulin lispro U-100, U-200 (Humalog)			
Insulin glulisine (Apidra)			
Short-acting Human Insulin			
Regular (Humulin R, Novolin R)	30–60 min.	2–4 hours	5–8 hours
Basal Insulin Products			
Intermediate-acting Human Insulin			
NPH (Humulin N, Novolin N)	2–4 hours	4–10 hours	10–24 hours
Long-acting Insulin Analogs			
Insulin glargine U-100 (Lantus, Basaglar, Semglee)	2–4 hours	No peak	20–24 hours
Insulin glargine U-300 (Toujeo)	6-hour	No peak	36 hours
Insulin degludec U-100, U-200 (Tresiba)	1-hour	No peak	42 hours
Combination Products			
70% NPH/30% regular (Humulin 70/30, Novolin 70/30)	30–60 min.	Dual	10–16 hours
75% NPL, 25% lispro (Humalog 75/25)	5–15 min.	Dual	10–16 hours
50% NPL, 50% lispro (Humalog 50/50)	5–15 min.	Dual	10–16 hours
70% insulin aspart protamine, 30% insulin aspart (Novolog 70/30)	5–15 min.	Dual	15–18 hours

[a] Peak and duration of insulin action are variable, depending on injection site, duration of diabetes, renal function, smoking status, and other factors.

[b] Onset of appearance is 2.5 minutes compared to 5.2 minutes for insulin aspart (NovoLog)

[c] Onset of appearance is 1 minute.

[d] Long-acting insulins are considered "peakless" although they have exhibited peak effects during comparative testing.

NPH, neutral protamine Hagedorn; *NPL*, insulin lispro protamine suspension

hypoglycemia, and glucose variability in patients with type 1 diabetes. Some CGM devices can integrate with an insulin pump in one system. These systems are referred to as AID systems and are discussed in more detail below. Current guidelines recommend CGM for patients on MDI or insulin pump therapy. CGM may be particularly useful for patients with hypoglycemia unawareness and/or frequent hypoglycemic events. Also see Chapter 5 (Diabetes Technology).

17. What is an automated insulin delivery system?

An automated insulin delivery system, also known as a closed-loop system, continuously monitors interstitial glucose levels via a CGM device and automatically adjusts insulin delivery through an insulin pump based on real-time glucose data using a control algorithm. This technology aims to maintain blood glucose levels within a target range, reducing the need for manual insulin adjustments. While each manufacturer's system is unique, there are some common features of most AID systems including automated basal insulin adjustments, automated correction boluses, and predictive alerts and alarms. Most systems still require the user to enter carbohydrate amounts to determine mealtime bolus doses. To date, we do not yet have an AID that truly functions as an artificial pancreas (a system that reads glucose levels and automatically delivers the right amount of basal and bolus insulin doses to maintain glycemic control), but the technology is getting closer. The four most advanced AID systems that are currently approved by the FDA are the Beta Bionics iLet, the MiniMed 780G, the Tandem TSlimX2 with Control-IQ, and the OmniPod 5.

TABLE 3.3 Currently Available Insulin Pumps and Continuous Glucose Monitors

	PRODUCT	COMPANY AND WEBSITE
Insulin pumps	MiniMed 630G, 770G	Medtronic Diabetes (www.medtronicdiabetes.com)
	Omnipod DASH	Insulet Corporation (www.omnipod.com)
	t:slim X2	Tandem Diabetes Care (www.tandemdiabetes.com)
Continuous glucose monitors	Dexcom G6 Dexcom G7	Dexcom (www.dexcom.com)
	FreeStyle Libre 14 FreeStyle Libre 2 FreeStyle Libre 2 Plus FreeStyle Libre 3 FreeStyle Libre 3 Plus	Abbott (www.freestyle.abbott/us-en/home.html)
	Eversense	Ascensia Diabetes Care (www.ascensiadiabetes.com/eversense/)
	Guardian Connect	Medtronic Diabetes (www.medtronicdiabetes.com)
AID systems	iLet Bionic Pancreas	Beta Bionics (www.betabionics.com)
	MiniMed 780G	Medtronic Diabetes (www.medtronicdiabetes.com)
	T:slim X2 with Basal IQ T:slim X2 with Control IQ Tandem Mobi	Tandem Diabetes (www.tandemdiabetes.com)
	Ominpod 5	Omnipod (www.omnipod.com)

AID, automated insulin delivery

Some people with type 1 diabetes are using "do-it-yourself" open-source insulin delivery systems which use a commercially available insulin pump and CGM device, with software algorithms that communicate with both. To learn more about available AID systems, refer to Table 3.3. Also see Chapter 5 (Diabetes Technology).

18. What are the patient's responsibilities before insulin pump therapy can be initiated?

- Commit at least 2–3 months to pump initiation and training, including multiple meetings with the diabetes team before, during, and after the pump is initiated.
- Demonstrate the ability to monitor BG values at least 4–10 times per day or use CGM, keep logs of BG readings, insulin doses, and food consumed, and communicate information to the team.
- Review pump training materials and practice pump functions at least two to three times before wearing the pump.
- Be willing to test basal rates or use CGM to ensure that the basal rates are set appropriately.

19. What are the benefits of insulin pump therapy?

Currently, insulin pump therapy is the dosing strategy that most closely mimics physiologic insulin secretion. Benefits over MDI include better, more precise glucose control with less glycemic variability, a reduction in frequency and severity of hypoglycemia, ability to adjust basal rates throughout the day (Fig. 3.2), ability to extend bolus dose durations to better cover high-fat meals (see Fig. 3.2), improved flexibility of lifestyle, ability to administer small amounts of insulin (as little as 0.025 units), protection from overcorrection by tracking active insulin, and ability to integrate with CGM technology. In addition, by continuously adjusting insulin delivery, AID systems can help maintain glucose levels within a target range and reduce the incidence of hyper- and hypoglycemia. AID systems may also reduce the burden of diabetes management.

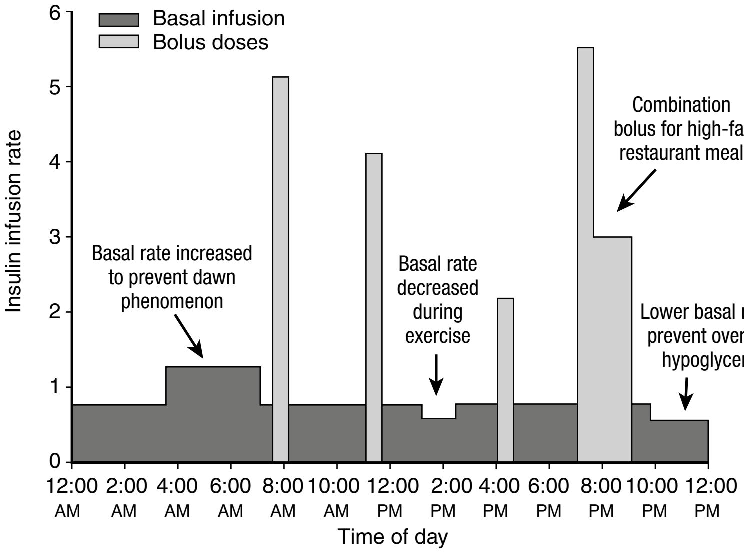

Fig. 3.2 Insulin delivery pattern with insulin pump therapy.

20. What are the limitations of insulin pump therapy?

The cost of an insulin pump and supplies is higher compared with that of an MDI regimen. The device must be worn 24 hours a day, and optimal use requires highly motivated, competent patients and a higher level of training. A strong support system from a diabetes team is beneficial. Other limitations include infusion site infections and risks of DKA if insulin delivery is interrupted.

21. What is carbohydrate counting, and how is it used with IIT?

Currently, carbohydrate counting is considered the "gold standard" for the estimation of mealtime insulin doses. Carbohydrate counting is a tool used to match bolus insulin doses to food intake because carbohydrates have the greatest effect on BG levels. The peak of bolus insulin analogs should match the peak of BG following carbohydrate digestion and absorption (approximately equal to 1–3 hours, depending on the fat and fiber content of the meal).

22. List the common foods that contain dietary carbohydrates.

- Starch: cereals, grains, beans, bread, rice, pasta, and starchy vegetables
- Sugar: lactose (milk and yogurt), fructose (fruit, juice, and honey), and sucrose (table sugar and desserts)
- Fiber: cellulose and hemicellulose, lignins, gums, or pectins found in fruits, vegetables, legumes, and whole grains

23. How are carbohydrates counted?

Calculating the number of carbohydrates may initially require measuring and weighing commonly eaten foods. Nutrition labels on the package state the number of grams of carbohydrates based on the serving size. Carbohydrate reference books are available at bookstores or through the American Dietetic Association (http://www.eatright.org) or the ADA; http://www.diabetes.org). Software programs are available for PDAs or online. Many restaurant chains provide nutrition brochures. See Chapter 6, for practical exercises in carbohydrate counting and insulin dosing.

24. What is the I:C ratio?

The I:C ratio is used to estimate how many grams of carbohydrate each unit of rapid-acting insulin will cover (e.g., 1:20 = 1 unit of bolus insulin is required to cover 20 g of carbohydrate consumed).

25. How do you determine an initial I:C ratio?

Ratios are based on a patient's weight and the total daily dose (TDD) of insulin, which usually indicates the patient's sensitivity to insulin. An MDI regimen of basal insulin and premeal injections of rapid-acting insulin must be previously (or concurrently) implemented before establishing an I:C ratio. A person must be taught to count carbohydrates before using an I:C ratio safely.

- Add up the patient's TDD of insulin on current therapy.
- Consider the A1C value (ADA target is <7%), frequency of hypoglycemia, and comorbidities.
- The initial I:C ratio is estimated in our practice by dividing 550 by the TDD. Example: 550 divided by 30 units = 1:18 I:C ratio.

In clinical practice, the constant in the I:C formula may range from 350 to 550. The initial calculated I:C must then be adjusted on the basis of each patient's records and is, therefore, only a starting point.

26. What is an example of an initial I:C ratio when changing to basal and bolus insulins?

- 40 units of Humulin 70/30 premixed insulin in the morning
- 17 units of Humulin 70/30 premixed insulin before the evening meal
- TDD = 57 units (A1C of 8.5% with two to three nocturnal hypoglycemic episodes per week)
- 550/57 = 9.6
- Begin with an I:C = 1:10

In this example, 1 unit of rapid-acting insulin will be given for every 10 g of carbohydrate eaten.

27. How do you adjust the I:C ratio once the initial ratio has been established?

Fine-tuning of an I:C ratio is based on BG records before meals and 2 hours after meals. The desired premeal BG is typically 80–130 mg/dL for most patients using IIT. An I:C ratio is correct if the BG increases by approximately 30–50 mg/dL over the premeal value at the 2-hour postprandial reading and returns to the range of 80–130 mg/dL by about 4–5 hours after the bolus insulin is given (Fig. 3.3). If 2-hour PPG level increments exceed 50 mg/dL, the I:C ratio should be adjusted, and testing repeated with further adjustments until the desired excursion is consistently achieved.

28. What are the common causes of high BG?

- Missing an injection or bolus dose of insulin
- Menstrual cycle

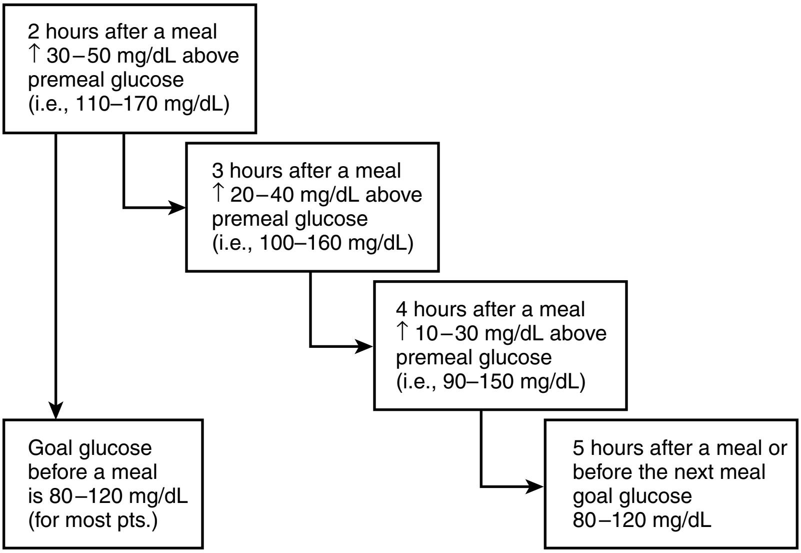
2 hours after a meal
↑ 30–50 mg/dL above
premeal glucose
(i.e., 110–170 mg/dL)
3 hours after a meal
↑ 20–40 mg/dL above
premeal glucose
(i.e., 100–160 mg/dL)
4 hours after a meal
↑ 10–30 mg/dL above
premeal glucose
(i.e., 90–150 mg/dL)
Goal glucose
before a meal
is 80–120 mg/dL
(for most pts.)
5 hours after a meal or
before the next meal
goal glucose
80–120 mg/dL

Fig. 3.3 Expected postprandial BG range with rapid-acting bolus insulin.

- Decreased activity
- Stress, illness, or infection
- Underestimating carbohydrates
- Steroids or other medications

29. What are other factors to consider when troubleshooting high BG readings?

- Dawn phenomenon: a rise in BG occurs in predawn hours because of increased growth hormone and cortisol production.
- Bad insulin: high BG occurs when insulin denatures if exposed to moderate-to-extreme temperatures or agitation, is beyond the expiration date, or the vial or pen device has been used for longer than the manufacturer's storage recommendations.
- Insulin pump or infusion set technical problems: settings programmed incorrectly; battery depleted; pump malfunctions; tubing incorrectly primed; air bubbles in the tubing; dislodged, bent, or kinked cannula; occlusion at the infusion site; infusion set in place >72 hours.

30. What causes high postprandial BG readings that are difficult to explain?

- Coffee (caffeine): a rise in BG after drinking coffee (including drinking it black, without cream or sugar) is seen in many patients' records and likely results from increases in epinephrine or free fatty acid mobilization and subsequent worsening insulin resistance.
- Cereal: a rise in BG is seen by patients consuming cereal, often requiring a lower I:C ratio (more insulin) and may be related to the glycemic index of most cereals combined with greater insulin resistance in the morning.
- Food-on-the-fingers: high BG readings occur from residual food or dextrose on fingers when testing (patients must wash hands or wipe off the first drop of blood.)
- Restaurant meals: Restaurant meals that are high in fat and calorically dense may require more insulin because of insulin resistance. A delay in digestion following a high-fat meal may require a split or extended bolus dose.

31. How is correctional insulin added for high BG before meals?

Correctional or supplemental insulin (high BG CF) is used to reduce high BG detected before meals. A high BG CF is the expected amount that one unit of insulin will decrease the BG under normal circumstances. It is determined by using a formula based on the person's insulin sensitivity. The initial CF is estimated in our practice by dividing 1650 by the TDD. In clinical practice, the constant in the CF formula may range from 1500 to 1800. The initial calculated CF must then be adjusted on the basis of each patient's records and is, therefore, only a starting point.

32. What is an example of determining an initial CF?

- 17 units of insulin glargine at noon and 5 units of insulin lispro before each meal
- TDD = 32 units (A1C of 7.2% with one to two hypoglycemic episodes per week)
- 1650/32 = 52
- Begin with a CF of 1:50

In this example, 1 unit of rapid-acting insulin will lower the BG about 50 mg/dL; therefore, 1 extra unit will be taken (in addition to the meal insulin dose) for each 50 mg/dL that the premeal BG is over the premeal goal of 100 mg/dL.

33. What is an example of I:C and CF usage?

To determine the amount of insulin needed before a meal, start with calculating the amount of bolus insulin needed to cover the meal. Example:

- I:C ratio is 1:20
- Meal consists of 80 g of carbohydrates
- Calculation: 80/20 = 4 units of insulin to cover the meal

Next, determine the amount of correctional insulin needed. If the BG is out of the target range before a meal, subtract the goal BG (100 mg/dL) from the actual BG and divide by the CF. Example:

- CF is 1:60
- Preprandial BG is 220 mg/dL
- Calculation: 220 – 100 mg/dL = 120 mg/dL above target

- Calculation: 120 (mg/dL)/60 = 2 units of insulin

In this example, the patient should take 6 units of bolus insulin before the meal—4 units to cover the carbohydrates in the meal and 2 units to return the premeal high BG to the target range.

34. When is a CF used?

- It is recommended that high BG corrections be taken before meals or at least 4 hours after the last bolus because of the duration of action of the bolus insulin analogues.
- Hypoglycemia may occur from the accumulation of active insulin if BG corrections are performed too frequently (stacking).

35. What can be done for a high postprandial BG reading?

- If a postprandial BG is dangerously high (i.e., >300 mg/dL) or a patient insists on making high BG corrections <4 hours since the last bolus or during the night, he or she should be instructed in how to take a partial correction for safety.
- Using one-half of the usual premeal CF to lower the BG to the target level is safest between meals.
- A target level of 150 mg/dL (expected BG level 2 hours postprandial) rather than a target BG of 100 mg/dL is used as the correction target between meals.

36. What is an example of using a half CF?

- BG before dinner = 100 mg/dL
- BG 2 hours after dinner = 300 mg/dL
- "Expected" BG 2 hours after dinner = approximately equal to 130–150 mg/dL
- Calculation: 300 minus 150 mg/dL = 150 mg/dL above target
- CF is 1:60
- Calculation: 150/60 = 2.5 units (full CF)
- The premeal insulin is still active for about 3 more hours; therefore, use a half CF.
- Calculation of half CF: 2.5 (units)/2 = 1.3 units

In this example, 1.3 units with an insulin pump or 1 unit with a syringe or insulin pen should be given 2 hours after the meal to bring the postprandial BG into the target range. BG should be rechecked within 2 hours to avoid a severe low glucose.

37. How do you calculate an initial basal rate for insulin pump therapy?

- An established C:I ratio and CF on MDI are critical for a smooth transition to pump therapy.
- To calculate an initial basal rate, take the current TDD of insulin on MDI, and reduce it by 25% (or other appropriate reduction, depending on current A1C and number of hypoglycemic episodes).
- Use 50% of this reduced dose as the new total basal dose to be given over 24 hours.
- Start with one basal rate for 24 hours (divide the total basal dose by 24).). [Initial basal rate per hour = (TDD × 0.75) ÷ (2 × 24).]
- The remaining 50% will be used as bolus doses for meals on the basis of carbohydrate counting.

38. Calculate an example of an initial basal rate for insulin pump therapy.

- Current TDD of insulin is 50 units. 25% reduction of TDD = 37.5 units
- 50% of reduced dose = 37.5/2 = 18.75 units as total basal
- Total basal insulin = 18.75/24 = 0.78 U/hour

In this example, the initial basal rate will be 0.8 U/hour. Basal rate adjustments will then be made on the basis of testing and recording BG profiles throughout the day.

39. How do you adjust basal rates in a person who is using an insulin pump?

Verify nighttime basal rates first. Nighttime basal rates should be adjusted before the daytime basal rates are verified. Testing is typically performed during the first week of insulin pump therapy. Be aware that patients transitioning from injected long-acting insulins (glargine or degludec) may have overlapping insulin activity, which may cause hypoglycemia during the first week. Testing is then repeated if a significant weight change occurs, if an exercise routine is begun or altered, following hormonal changes (e.g., puberty, menopause), or as needed. Here are the instructions for the patient to use when verifying overnight basal rates:

- Assess basal rate accuracy on three nights.

- Eat the evening meal early, preferably before 5:00 p.m. (or begin the test period ≈ 5 hours after eating), and take the usual insulin bolus for dinner and correction, if needed.
- Choose a meal that you frequently eat or one for which you are confident of the carbohydrate amount.
- Avoid meals with >15–20 g of fat, 10 g of fiber, and alcohol on testing nights.
- Avoid any food or insulin bolus after the evening meal.
- Avoid exercise other than typical activity.
- Monitor BG before and 2 hours after the evening meal, at 9:00 p.m., 12 midnight, 3:00 a.m., 6:00 a.m., and before breakfast (or use CGM during this time).
- Stop the test if BG is <70 mg/dL or >250 mg/dL during the basal test and treat the abnormal BG.

Adjust nighttime basal rates based on the following parameters:

- If BG levels change by >20–30 mg/dL during overnight monitoring, adjust the basal rate for the next night by 0.1 U/hour, starting 1–3 hours before the BG change was seen.
- Changes are made until the FBG level in the morning is within the target range (80–130 mg/dL).
- Daytime basal rates are verified next, usually 1–2 weeks after pump initiation or as necessary.

After nighttime basal rates have been confirmed, you can move on to daytime basal rate adjustments.

- Have patients skip breakfast and check their BG levels every hour from 7:00 a.m. to 12 noon (or use a CGM) to verify the morning basal rate.
- If BG levels change by >20–30 mg/dL during this time, adjust the basal rate for the next day by 0.1 U/hour, starting 1–3 hours before the glucose change was seen.
- After the morning basal rate is set, have patients skip their other meals (on separate days), and follow the same monitoring and adjustment procedures to confirm the afternoon and evening basal rate(s).

For patients who are using an AID, the algorithm will adjust basal rates based on glucose patterns. At each visit, the clinician can compare the basal rate settings with the actual daily amount of basal insulin used and adjust the settings to align with actual basal needs.

40. What is the role of noninsulin medications in the treatment of type 1 diabetes?

Pramlintide, an amylin analog, delays gastric emptying, decreases inappropriate glucagon secretion from the pancreas after a meal and increases satiety. It is approved for use as an adjunct to insulin therapy in patients with type 1 diabetes who have failed to achieve desired glycemic control despite optimal insulin therapy. Pramlintide has been shown to induce weight loss and lower insulin doses. It is administered before meals and concurrent reduction of meal-time bolus insulin dosing is required to reduce the risk of hypoglycemia.

Metformin, glucagon-like protein 1 (GLP1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors may reduce insulin requirements and improve metabolic control in patients with type 1 diabetes. Several medications in these classes have been or are being studied in patients with type 1 diabetes, but none have been approved by the FDA for use in type 1 diabetes.

41. What is the recommended treatment of hypoglycemia?

Dextrose should be taken for a BG <70 mg/dL. She/he should take 15 g of a quick-acting carbohydrate: fruit juice, glucose tablets or gel, or dextrose-based candy (SweetTARTS, Smarties, Sprees). Pure glucose (without added fat or protein) is preferred. They should wait 15 minutes and test BG again. If repeat BG is <70 mg/dL, additional dextrose should be taken. Once glucose returns to normal, she/he should eat a meal or snack to prevent recurrent hypoglycemia.

42. Why does rebound hyperglycemia occur after hypoglycemia?

- Overtreatment with an inappropriate amount of carbohydrate often occurs.
- No treatment (i.e., sleeping through a low glucose episode) may result in acute counterregulatory hormone (glucagon, epinephrine, cortisol, growth hormone) release resulting in increased hepatic glycogenolysis and gluconeogenesis.
- Treatment with foods that contain fat delays digestion and absorption, thereby prolonging hypoglycemia and causing counterregulatory hormone release with subsequent hepatic glycogenolysis.

43. Discuss the use of glucagon to treat severe hypoglycemia.

All patients who are at risk for hypoglycemia, which includes those using MDI or pump therapy, should be given a glucagon prescription and a demonstration. Glucagon is used to raise BG when a person is unable or unwilling to consume carbohydrates by mouth. This may occur either as a result of a seizure or unconsciousness. Family members should receive instruction, and the patient should be able to demonstrate the procedure to a third party (coworker or neighbor). Currently, available glucagon products include an injection powder with diluent for reconstitution, a nasal powder, and a prefilled injection pen. The nasal powder and prefilled pen are often preferred because they are easier to use. However, cost can be a barrier so it's important to check a person's insurance coverage and prescribe formulary products when possible.

KEY POINTS

Intensive insulin therapy

- Studies have demonstrated that optimal diabetes management decreases chronic complications.
- Intensive insulin therapy, or basal-bolus therapy, is required to mimic normal pancreatic insulin secretion.
- Basal insulin is physiologic insulin required to manage BG fluctuations due to hepatic glucose production.
- Bolus insulin is matched to carbohydrate intake using a carbohydrate-to-insulin ratio.
- Correctional bolus insulin reduces the BG to within normal limits when a high glucose correction factor is used.
- Advances in technology are improving intensive insulin therapy. AID systems that use continuous glucose monitoring data to automatically adjust insulin delivery via an insulin pump in real-time provide better glucose control with less hypoglycemia.

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Type 2 Diabetes Mellitus

Jennifer M. Trujillo

CHAPTER 4

1. What are the standards of care for the management of type 2 diabetes (T2D)?

Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have published evidence-based minimum standards of diabetes care. Both sets of standards include recommendations on the screening, diagnosis, classification, prevention, and management of diabetes, including lifestyle modifications, glycemic treatment, cardiovascular (CV) risk management, prevention and treatment of complications, and glycemic management in specific populations and practice settings. Both recommend that patients have a comprehensive medical evaluation and assessment of comorbidities at each visit. The standards from both organizations are evidence-based, frequently updated, and easily accessible. The ADA Standards of Care are available at: https://professional.diabetes.org/standards-of-care and the AACE guidelines are available at: https://pro.aace.com/clinical-guidance/2023-aace-consensus-statement-comprehensive-type-2-diabetes-management-algorithm.

2. What should be included in a comprehensive evaluation of a person with T2D?

At the initial visit, a complete diabetes and medical history, family history, and personal history of complications and common comorbidities should be completed. Lifestyle and behavior patterns, as well as glucose monitoring, need to be assessed initially and at every visit. A medication history is essential and should include medication–taking behaviors, intolerances, complementary and alternative medicine use, and vaccination history. A complete physical examination, including vital signs, thyroid palpation, skin examination, and comprehensive foot examination, should be performed. Referral for an ophthalmologic examination and, if appropriate, smoking cessation counseling are also recommended. Overall glycemic control, including a glycosylated hemoglobin (HbA_{1C}), should be assessed initially and every 6 months in patients with adequate glycemic control and every 3 months in patients not achieving glucose targets.

Laboratory data that are recommended at the initial visit and annually thereafter include a lipid panel, liver function tests, spot urine albumin-to-creatinine ratio, serum creatinine and estimated glomerular filtration rate (eGFR), vitamin B_{12} (if on metformin), and serum potassium (if on an angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB], or diuretic). Screening for psychosocial conditions, self-management education needs, hypoglycemia, and pregnancy planning should be performed. Atherosclerotic cardiovascular disease (ASCVD) risk assessment and staging of chronic kidney disease (CKD) are also recommended. Patient-specific, individualized goals should be set for HbA_{1C}, blood pressure (BP; for those with hypertension [HTN]), and self-management behaviors.

3. What are the goals of therapy for people with T2D?

The primary goals of therapy for T2D are to prevent or delay the progression of long-term microvascular and macrovascular complications, including retinopathy, neuropathy, diabetic kidney disease (DKD), and ASCVD. Additional goals of therapy are to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse medication effects, minimize treatment burden, and maintain quality of life. To achieve these goals, several organizations, including the ADA and AACE, recommend surrogate targets for glycemic control. The ADA Standards of Care indicate that an A1C target should be established for each patient; HbA_{1C} <7% is reasonable for most nonpregnant adults, but the HbA_{1C} goal should be individualized on the basis of patient-specific factors (see Section 5, How should glycemic targets be established?). A fasting plasma glucose (FPG) target range of 80–130 mg/dL and a postprandial glucose (PPG) target of <180 mg/dL (1–2 hours after the beginning of a meal) correspond with an HbA_{1C} target of <7%. The AACE guidelines are more aggressive and indicate that HbA_{1C} ≤6.5% is optimal if it can be achieved in a safe and affordable manner. An FPG target of <110 mg/dL and a 2-hour PPG target

TABLE 4.1 Glycemic Target Recommendations for Most Nonpregnant Adults With Diabetes[a]

	ADA	AACE
HbA_{1C}	<7.0%	≤6.5%
FPG	80–130 mg/dL	<110 mg/dL
PPG	<180 mg/dL	<140 mg/dL

[a] Glycemic targets should be individualized. More or less stringent goals may be appropriate for some patients.
AACE, American Association of Clinical Endocrinologists; *ADA*, American Diabetes Association; *HbA_{1C}*, glycosylated hemoglobin; *FPG*, fasting plasma glucose; *PPG*, postprandial glucose.

of <140 mg/dL correspond with this recommendation (Table 4.1). For patients that are using continuous glucose monitoring, an A1C target <7% coincides with a target time in range >70%.

4. What is the evidence to support tight glycemic control?

The United Kingdom Prospective Diabetes Study (UKPDS) was a landmark trial evaluating the impact of intensive glucose control on the incidence of long-term complications in patients with T2D. Investigators recruited 5102 patients with newly diagnosed T2D in 23 centers within the United Kingdom between 1977 and 1991. Patients were followed up for an average of 10 years to determine the impact of intensive versus conventional glycemic control. The results showed that the intensive glycemic control arm achieved an HbA_{1C} of 7% compared with 7.9% in the conventional group. This translated into a 12% reduction in the primary composite endpoint of any diabetes–related complication ($P = 0.029$). Most of this resulted from a 25% reduction in microvascular complications in patients assigned to the intensive treatment arm compared with those in the conventional arm. There was also a 16% reduction in ASCVD events in the intensive group, but this did not quite reach statistical significance ($P = 0.052$). The microvascular benefits of early glucose control persisted 10 years after the end of the original trial. The 10-year follow-up report also showed a significant long-term reduction in myocardial infarction (MI) and all-cause mortality.

Three additional large-scale studies were performed after the UKPDS to compare the effects of different intensities of glycemic control on the risk of macrovascular complications. These studies included patients who had long-standing, advanced T2D and were at high risk for ASCVD; in contrast, the UKPDS included subjects with newly diagnosed T2D. The action to control cardiovascular risk in diabetes (ACCORD) study (n = 10,251) showed that lower HbA_{1C} levels (achieved mean HbA_{1C} 6.4% versus 7.5%) reduced the risk of some microvascular complications but did not reduce the risk of macrovascular complications. The risk of hypoglycemia was significantly higher in the intensive treatment group. Most importantly, this study was stopped early because of an increase in mortality in the intensive treatment arm. The action in diabetes and vascular disease: preterax and diamicron modified release-controlled evaluation (ADVANCE) study (n = 11,140) similarly showed no significant differences in ASCVD outcomes between two levels of glycemic control (achieved mean HbA_{1C} 6.3% versus 7%) but did show that more intensive glucose control reduced microvascular complications. The Veterans Affairs diabetes trial (VADT; n = 1791) also suggested reduced microvascular complications but reported no significant reduction in ASCVD outcomes with more intensive glycemic control (HbA_{1C} 6.9% versus 8.5%). On the basis of the results of these studies in aggregate, the relatively intense effort required to achieve more stringent glucose control should be considered when setting targets.

5. How should glycemic targets be determined?

Glycemic targets must be individualized for each person based on patient-specific factors and the potential risks and benefits of treatment. Ideally, glycemic targets should be established at the time of diagnosis and should be reviewed and reevaluated at each visit. When possible, these decisions should be made in collaboration with the patient. Patient or disease factors to consider include the following: treatment–related risks, such as hypoglycemia and other adverse medication effects; disease duration; life expectancy; comorbidities; established vascular complications; patient attitude and expected treatment effort; resources; and a support system. Although an HbA_{1C} <7% is recommended by the ADA for most nonpregnant adults with T2D, a more stringent goal (e.g.,

<6.5%) may be appropriate for some patients if it can be achieved without significant adverse effects, particularly hypoglycemia. Those patients might be younger, have a longer life expectancy, have a short duration of diabetes, be treated only with lifestyle modifications or metformin, or be without significant comorbidities. Less stringent goals (e.g., <8%) may be appropriate for older patients, those with a limited life expectancy, those with a long duration of diabetes, those with a history of severe hypoglycemia, and those with extensive serious comorbidities or advanced complications. A higher HbA_{1C} goal may also be appropriate when it is difficult to achieve the goal despite appropriate education, monitoring, and drug therapy. For those treated with complex medication regimens, especially those that include insulin, the risks in attempts to achieve stringent glycemic goals may outweigh the benefits.

Higher HbA_{1C} goals should be considered in patients >65 years of age. An HbA_{1C} goal of <7.5% is reasonable for healthy older adults, whereas an HbA_{1C} goal of <8% is reasonable for older adults with multiple coexisting chronic diseases, multiple impairments of activities of daily living (ADLs), or mild-to-moderate cognitive impairment. An HbA_{1C} goal of <8.5% is reasonable for older adults with end-stage chronic diseases, multiple dependencies for ADLs, or moderate-to-severe cognitive impairment or for those who live in long-term care facilities. Clinicians should consider adjusting the FPG and PPG target ranges to correspond with a higher target HbA_{1C}.

6. What lifestyle modifications are recommended for patients with T2D?

All patients with T2D should participate in diabetes self-management education (DSME) to acquire the knowledge, skills, and abilities needed for self-care. DSME should occur at the time of diagnosis, annually, when complicating factors arise, and when transitions of care occur. The goals of nutrition therapy are to promote and support healthy eating patterns; achieve and maintain body weight goals; achieve individualized glycemic, blood pressure, and lipid goals; and delay or prevent the complications of diabetes. Nutrition recommendations should be individualized on the basis of needs, social determinants of health, personal and cultural preferences, health literacy and numeracy, and willingness and ability to make changes. Healthy eating and meal plans should focus on eating more nutrient-dense foods (e.g., vegetables), eating less saturated fat and added sugar, eating a variety of foods, decreasing empty calories (e.g., candy, sweets, sugar-sweetened beverages), making half of the grain consumption be from whole grains, and shifting to lower-fat dairy products.

Weight loss of at least 5% of body weight should be recommended initially for any patient who is overweight or obese. Clinical benefits of weight loss are progressive, and more aggressive weight loss goals may be appropriate. Newer medications may help patients achieve more substantial and sustainable weight loss. Evidence supports focusing on a reduction in calorie intake instead of macronutrient distribution. Studies have shown that reduced calorie interventions reduce HbA_{1C} by 0.3–2% in patients with T2D. Weight loss can be attained by reducing portion sizes, reducing calorie intake by 500–750 kcal/day, or by targeting daily caloric intake goals to less than 1200–1500 kcal/day for women and 1500–1800 kcal/day for men.

Carbohydrate counting can be a useful tool for minimizing postmeal glucose excursions. Patients should be educated about which foods are sources of carbohydrates and that carbohydrates are the nutrient group that increases blood glucose (BG) levels. The diabetes plate method can be used to help patients identify a reasonable amount of carbohydrate intake per meal and to encourage them to limit their starch or grain consumption to one-fourth of a 9-inch plate per meal. A common but more complex approach is to provide more specific carbohydrate serving limits to patients: limit carbohydrates to 2–3 servings (30–45 g) per meal for women or 3–4 servings (45–60 g) per meal for men and 1 serving (15 g) per snack. Individuals with T2D who are taking mealtime insulin may be instructed on how to count carbs to determine their premeal insulin dose. Although this is a more common practice in type 1 diabetes (T1D), it may be beneficial in patients with T2D who are on intensive insulin regimens.

Adults with T2D should engage in 150 minutes or more of moderate- to vigorous-intensity aerobic activity per week with no more than 2 consecutive days without activity. Patients should decrease the amount of sedentary time and avoid prolonged periods of sitting. Adults with T2D who are overweight or obese and have achieved short-term weight loss goals should participate in 200–300 minutes of physical activity per week as part of a comprehensive, long-term weight maintenance program.

7. What is the initial management of T2D?

There are many classes of medications recommended by current practice guidelines and standards of care for the management of T2D, including metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP1 RAs), GLP1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, dipeptidyl peptidase 4 (DPP4) inhibitors, thiazolidinediones (TZDs), sulfonylureas, and insulin. Mechanisms, physiologic actions, and renal dosing recommendations of each drug category are summarized in Table 4.2. Initial management of T2D has traditionally included metformin. Now, due to evidence related to cardiovascular and kidney outcomes with other agents, decisions on the treatment of T2D should be made based on the presence of comorbidities including ASCVD, heart failure, and chronic kidney disease. Agents that have evidence for reducing cardiovascular, heart failure, and kidney–related outcomes should be prioritized. Although metformin is no longer promoted by clinical guidelines as the clear first-line therapy option, it still remains a common cornerstone of medication regimens for T2D.

8. What is metformin?

Metformin is a biguanide, which is an oral agent that decreases glucose production by the liver, reduces the amount of glucose absorbed from the intestines, and improves the body's sensitivity to insulin. Metformin was considered first-line therapy for T2D for years because of its high glucose-lowering effect; strong evidence to support its use, including a reduced risk of CV outcomes, as shown by the UKPDS trial; neutral effect on weight; low risk of hypoglycemia; good safety profile; low cost; and ease of administration. The most common side effects of metformin are gastrointestinal (GI) in nature and include diarrhea, nausea, vomiting, and flatulence. To minimize these side effects, metformin should be initiated at a low dose and titrated up in a stepwise fashion. The target dose of metformin is 2000 mg/day (usually given in two divided doses); however, this is not the starting dose. Metformin should be initiated at 500 mg orally daily and titrated up by 500 mg each week until a maximum tolerated dose or 2000 mg daily is achieved. Other strategies for minimizing GI–related side effects of metformin include taking metformin with food and using an extended-release (ER) preparation; an important patient-counseling point when using the ER preparations is that patients may see parts of the ER tablets in their stool.

Metformin also reduces intestinal absorption of vitamin B_{12} and may lower serum B_{12} concentrations. The longer the duration of metformin use, the more likely it is that B_{12} deficiency will occur. Because of the insidious onset of B_{12} deficiency, it is recommended that serum B_{12} levels be monitored every 2–3 years and treated accordingly. Severe vitamin B_{12} deficiency may present as peripheral neuropathy (PN). If the symptoms of PN are present and the patient is taking metformin, the B_{12} level should be checked to determine whether the symptoms are caused by B_{12} deficiency or by the progression of diabetes or another cause.

9. What is SGLT2 inhibitor?

SGLT2 inhibitors prevent the kidneys from reabsorbing glucose from urine in the proximal tubules back into the bloodstream, leading to increased glucose excretion in urine. This results in lowering of both FPG and PPG and modest weight loss caused by the loss of glucose (4 kcal/g) in urine. Because of their mechanism of action, SGLT2 inhibitors do not require insulin or functional beta cells to be effective.

SGLT2 inhibitors have demonstrated benefits in reducing major adverse cardiovascular events (MACE) in patients with T2D and ASCVD. They have also demonstrated benefits in reducing heart failure–related outcomes in patients with heart failure with or without T2D and at slowing the progression of CKD in patients who have T2D and CKD. Currently available SGLT2 inhibitors include canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and bexagliflozin.

10. What are the side effects associated with SGLT2 inhibitors?

The excess urinary glucose increases the risk of genital mycotic and urinary tract infections, some of the more common side effects of this class of medications. The presence of more glucose in urine also causes osmotic diuresis, which can lead to increased urination and a small reduction in BP. Dizziness and orthostatic hypotension could occur, so it is important to counsel patients to stay well hydrated and stand up slowly when they initiate SGLT2 inhibitor therapy. SGLT2 inhibitors are associated with an increased risk of diabetic ketoacidosis, particularly in people

TABLE 4.2 Mechanisms and Physiologic Actions of Common Glucose-Lowering Agents to Treat TD2

CLASS	COMPOUND(S)	RENAL DOSING RECOMMENDATIONS	CELLULAR MECHANISM(S)	PRIMARY PHYSIOLOGIC ACTION(S)
Biguanides	Metformin	Do not initiate if eGFR 30–45 Do not use if eGFR <30 If eGFR drops to <45 and metformin is continued, consider a maximum of 1000 mg daily	Activates AMP kinase (? Other)	↓ Hepatic glucose production
SU; second generation	Glyburide Glipizide Glimepiride	Avoid use in renal impairment (glyburide); initiate conservatively to avoid hypoglycemia	Closes KATP channels on beta cell plasma membranes	↑ Insulin secretion
TZD	Pioglitazone Rosiglitazone	No dose adjustment required	Activates the nuclear transcription factor PPAR-gamma	↑ Insulin sensitivity
DPP4 inhibitors	Sitagliptin Saxagliptin Linagliptin Alogliptin	Adjust dose if eGFR ≤50 (sitagliptin, saxagliptin); eGFR ≤60 (alogliptin); no dose adjustment needed (linagliptin)	Inhibits DPP4 activity, increasing postprandial incretin (GLP1, GIP) concentrations	↑ Insulin secretion (glucose-dependent); ↓ glucagon secretion (glucose-dependent)
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Bexagliflozin	Glycemic efficacy is reduced if eGFR <45 (all agents); Adjust dose if eGFR 30–60, do not initiate if eGFR <30 (canagliflozin, bexagliflozin); do not initiate if eGFR <25 (dapagliflozin), no restrictions (empagliflozin); Do not initiate or use if eGFR <45 (ertugliflozin)	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glycosuria
GLP1 receptor agonists and GLP1/ GIP receptor agonist	Dulaglutide Exenatide Exenatide XR Liraglutide Lixisenatide Semaglutide Semaglutide Oral Tirzepatide	Limited experience with severe renal impairment; avoid use if eGFR <30 (exenatide, exenatide XR), eGFR <15 (lixisenatide); no dose adjustment recommended (dulaglutide, semaglutide)	Activates GLP1 receptors	↑ Insulin secretion (glucose-dependent); ↓ Glucagon secretion (glucose-dependent); Slows gastric emptying; ↑ Satiety
Basal Insulin	Degludec Glargine U-100 Glargine U-300	Lower insulin doses may be required with decreased eGFR	Activates insulin receptors	↑ Glucose disposal; ↓ Hepatic glucose production; Suppresses ketogenesis

AMP, Adenosine monophosphate; *eGFR*, estimated glomerular filtration rate; *GIP*, glucose-dependent insulinotropic polypeptidase; *PPAR*, peroxisome proliferator-activated receptor; *XR*, extended release, *TD2*, type 2 diabetes*;* *SU,* sulfonylureas; *TZD*, thiazolidinediones; *DPP*, dipeptidyl peptidase; *SGLT*, sodium-glucose cotransporter; *GLP*, glucagon-like peptide.

with T1D and in the perioperative population. Rates in adults with T2D are low and range from 0.16–0.76 events per 1000 patient-years. In T2D, the risk is increased in people who are insulin deficient, in older people, or in those with prolonged use of SGLT2 inhibitors. Patients with a higher risk for DKA with SGLT2 inhibitors should be informed of the importance of adherence to insulin treatment and avoiding very low-carbohydrate diets (such as ketotic diets) and excessive intake of alcohol. Education on the management of sick days should also be given, and basal insulin doses should not be discontinued completely.

11. What is a GLP1 RA?

GLP1 RAs are also known as *incretin mimetics*. These agents mimic the effects of endogenous incretins (specifically, GLP1) in the body by (1) stimulating insulin secretion after eating, (2) inhibiting glucagon release, and (3) slowing gastric emptying, which increases satiety earlier and slows glucose absorption into the blood. GLP1 RAs cause weight loss because of their effects on gastric emptying and early satiety; some of the agents are approved for weight management under different trade names in people who are overweight or obese with or without T2D. Most of the available products are administered subcutaneously with an injectable pen device; however, one agent is also available as an oral formulation taken once daily. Currently available GLP1 RAs include exenatide (twice daily), liraglutide (once daily), lixisenatide (once daily), exenatide extended-release (once weekly), dulaglutide (once weekly), semaglutide (once weekly), and oral semaglutide (once daily). Liraglutide and lixisenatide are also available in fixed-ratio combinations with basal insulin (degludec and glargine, respectively). Some of these agents (liraglutide, dulaglutide, and semaglutide) have demonstrated CV benefit in people with T2D and established CV disease or high CV risk. Subcutaneous semaglutide also has demonstrated benefits at slowing the progression of CKD in patients with T2D and CKD.

Exenatide and lixisenatide are short-acting GLP1 RAs that have more pronounced PPG-lowering effects, especially after a meal that immediately follows the injection. This contrasts with the long-acting GLP1 RAs, liraglutide (once daily), dulaglutide, exenatide extended release, and semaglutide (all once-weekly dosing), which lower FPG in addition to their PPG effects.

12. What are the side effects associated with GLP1 RAs?

Because these agents promote glucose-dependent insulin secretion (insulin secretion only occurs when BG levels are high or rising), their risk of hypoglycemia is low when used as monotherapy or with other agents, such as metformin, for which the risk of hypoglycemia is also low. However, their use in conjunction with agents known to cause hypoglycemia may increase this risk.

The most common side effects of GLP1 RAs are GI related, with nausea being the most common. This underscores the importance of titration to target doses in a stepwise fashion to minimize this risk. Fixed-ratio combinations of GLP1 RAs and basal insulin (liraglutide plus degludec, lixisenatide plus glargine), which are appropriate for patients requiring combination therapy for better glycemic control, minimize this side effect, because the titration of the GLP1 RA dose is much more incremental than with a GLP1 RA alone. If a long-acting GLP1 RA dose is missed, retitration may be necessary.

These agents may be associated with acute pancreatitis; however, there is not enough evidence to prove a cause-and-effect relationship. Nonetheless, a GLP1 RA should not be initiated in patients with active pancreatitis or a history of pancreatitis related to a GLP1 RA. If pancreatitis is suspected while a patient is using a GLP1 RA, the drug should be discontinued. If the patient is confirmed to have pancreatitis related to the GLP1 RA, the patient should not be rechallenged with a drug from this class. GLP1 RAs are also associated with an increased risk of gallbladder or biliary disease, including cholelithiasis and cholecystitis. The overall risk seems low but appears higher with higher drug doses, longer duration of use, and when the agents are used for weight loss rather than glucose control.

A significant increase in retinopathy complications was seen in people taking semaglutide during the SUSTAIN-6 (trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with T2D) trial. Meta-analyses have not produced consistent results to determine if this should be considered an adverse effect for the GLP1 RA class. The mechanism is also not fully understood; it could be due to the medication itself or due to rapid glucose lowering, or a combination. Caution should be taken when starting a GLP1 RA in someone with preexisting diabetic retinopathy and patients should be monitored closely for retinopathy complications.

A large randomized controlled trial (a research study to look at how semaglutide compared to placebo affects diabetic eye disease in people with T2D [FOCUS], NCT03811561) evaluating the long-term effects of subcutaneous semaglutide on eye disease in people with T2D is ongoing and should provide more evidence.

A rare but important potential side effect of GLP1 RAs is thyroid C-cell tumors. Patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia-2 (MEN-2) should not be prescribed a GLP1 RA.

13. What is a GLP1/GIP RA?

A GLP1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist (GLP1/GIP RA) is similar to the GLP1 RA medication class, except that it is a dual-acting agent that targets both GLP1 and GIP receptors. GIP is another hormone involved in blood glucose homeostasis. This class has a similar mechanism of action as GLP1 RAs but may have higher glucose and weight loss benefits. Tirzepatide is the first approved medication in this class and is currently approved for the treatment of T2D and for chronic weight management in patients who are overweight or obese. The cardiovascular outcome trial for tirzepatide is still ongoing, thus the potential cardiovascular benefit of tirzepatide is still not known.

14. What is a DPP4 inhibitor?

Dipeptidyl peptidase 4 (DPP4) inhibitors work by blocking DPP4, which is an enzyme responsible for breaking down GI incretins (including GLP1 and GIP). DPP4 inhibitors increase circulating levels of endogenous incretin hormones, which then promote glucose-dependent insulin secretion and inhibit glucagon secretion. However, in contrast to GLP1 RAs, they do not affect gastric emptying or satiety, and thus the glycemic-lowering effect of DPP4 inhibitors is modest, and they are weight neutral as opposed to promoting weight loss. Benefits of these agents include their good tolerability, low risk of hypoglycemia, and their ability to target PPG. Examples of medications in this class include alogliptin, linagliptin, saxagliptin, and sitagliptin; all have similar glycemic efficacy.

Cardiovascular outcomes trials (CVOTs) of DPP4 inhibitors have been largely neutral; that is, there are generally no cardiovascular disease (CVD) concerns, but no CV benefits have been reported either. Saxagliptin is the exception; the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial showed an increased risk of hospitalizations for heart failure. Because of this, all DPP4 inhibitors now carry a warning about use in patients at risk for heart failure.

In general, DPP4 inhibitors are well tolerated, and their risk of adverse effects is low. Like GLP1 RAs, DPP4 inhibitors have been associated with an increased risk of pancreatitis. DPP4 inhibitors should be avoided in patients with active pancreatitis or a history of pancreatitis thought to have been caused by a DPP4 inhibitor. If a patient develops pancreatitis while taking one of these agents, the DPP4 inhibitor should be discontinued. If the DPP4 inhibitor is implicated in causing pancreatitis, a drug from this class should not be used for the patient. Additionally, DPP4 inhibitors have been associated with an increased risk of joint pain; if this occurs, the DPP4 inhibitor should be discontinued, and symptoms should resolve. DPP4 inhibitors have also been implicated in cases of bullous pemphigoid.

15. What is a TZD?

Thiazolidinediones (TZDs) are a class of agents that target the peroxisome proliferator-activated receptor (PPAR) gamma, which activates the genes that influence insulin-mediated glucose metabolism and how fat is stored in the body. These agents, pioglitazone and rosiglitazone, improve insulin sensitivity in muscle and fat tissue and protect pancreatic beta cells. TZDs predominantly improve FPG. Because of their effects on gene activation, they have a slow onset of action; it typically takes several weeks for their full glycemic effects to be realized.

The use of rosiglitazone has fallen out of favor because of a meta-analysis that showed it to be associated with a statistically significant increased risk of MI and nonstatistically significant increased risk of death. Pioglitazone has been associated with a potential increased risk of bladder cancer, although clinical trial data regarding this risk are inconsistent. Both agents are known to cause dose–related edema and should not be used in patients with symptomatic heart failure.

16. What is a sulfonylurea?

Sulfonylureas (SU) that are most commonly in use today are glipizide, glyburide, and glimepiride. Sulfonylureas—also known as insulin secretagogues—are oral agents that work by stimulating endogenous insulin secretion by the pancreatic beta cells. Because of this, sulfonylureas are only useful in patients with some residual beta cell function. These agents predominantly lower PPG but also positively affect FPG. Side effects of sulfonylureas include weight gain and hypoglycemia. Although sulfonylureas contain a sulfonamide structure, the cross-reactivity between this type of sulfonamide and an antibiotic sulfonamide is significantly low.

Glipizide and glimepiride are shorter-acting than glyburide and, therefore, may cause less hypoglycemia. In addition, glyburide is excreted renally and its active metabolites may accumulate in patients with renal dysfunction, again leading to hypoglycemia. Glipizide and glimepiride, in contrast, are metabolized by the liver and primarily excreted via urine as inactive metabolites, making them a preferred choice in patients with diabetes and CKD. Of note, micronized products are not bioequivalent, and retitration may be needed when switching between products.

17. What is basal insulin?

Basal insulin, also called "background insulin," is designed to provide 24-hour glycemic control by suppressing hepatic glucose production and maintaining near-normal glucose levels in the fasting state when taken in appropriate doses. Basal insulin is used in patients with T2D to supplement their endogenous insulin production. This option may be a first-line choice for patients whose HbA_{1C} is well above the goal (e.g., ≥10%) and is an effective second-line choice if a patient does not achieve glycemic targets on maximum-dose metformin.

The currently available basal insulins include long-acting agents (degludec [U-100 and U-200], glargine [U-100 and U-300], and intermediate-acting NPH (see Chapter 3, Table 3.1 for a complete list of products and their pharmacodynamics [PD])). Insulin detemir was a commonly used basal insulin for years but was discontinued by the manufacturer in 2024. All basal insulins are effective at lowering FPG levels and HbA_{1C}. Each has an onset of action of approximately 2 hours, but the duration of action varies among the agents; for example, insulin degludec has a duration of over 40 hours, whereas neutral protamine Hagedorn (NPH) insulin lasts approximately 12 hours and is typically dosed twice daily. Newer agents, such as degludec and glargine U-300, have longer durations of action and minimal or no peaks, which has translated into more consistent pharmacokinetics (PK) and PD, less nocturnal hypoglycemia, and more dosing flexibility compared with older agents such as glargine U-100 and NPH.

The main side effects associated with basal insulin are hypoglycemia and weight gain. Using basal insulin in combination with certain oral or injectable agents known to be weight neutral or to promote weight loss may both mitigate weight gain and minimize the dose of insulin required, decreasing the risk of hypoglycemia. Stepwise titration of basal insulin also minimizes the risk of hypoglycemia.

18. What other diabetes medications are available?

In addition to the agents already discussed, there are several other classes of oral diabetes medications that are less frequently used in practice. Meglitinides (repaglinide and nateglinide) enhance endogenous insulin secretion (secretagogues) and thereby reduce postprandial hyperglycemia, similar to the sulfonylureas. Meglitinides have a more rapid onset and are shorter-acting than sulfonylureas. Meglitinides may have a role in patients with true allergies to sulfonylureas because they work similarly and have comparable HbA_{1C}-lowering ability; however, they are more expensive and must be taken before all meals.

Alpha-glucosidase inhibitors (miglitol and acarbose) have modest HbA_{1C}-lowering efficacy (0.5–0.8%) and work by slowing the absorption of dietary carbohydrates. Because of their mechanism of action, the hallmark side effect of these medications is GI intolerance, including flatulence and diarrhea, and many patients do not tolerate these effects.

Colesevelam, a bile acid sequestrant, modestly improves HbA_{1C} (approximately 0.5%) by decreasing bile acid reabsorption. It is unknown how this effect on reabsorption decreases BG. An added benefit is that in addition to lowering BG, it lowers low-density lipoprotein cholesterol (LDL-C).

Last, the immediate-release dopaminergic agonist bromocriptine also lowers BG by activating central dopamine-2 receptors and increasing insulin sensitivity. Like colesevelam, its effect on HbA_{1C} lowering is modest. It is not commonly used because of its high cost and its side effect profile (dizziness, nausea, and fatigue).

19. What is the general approach to the treatment of T2D?

The general approach to glycemic management in nonpregnant adults with T2D includes prompt initiation of lifestyle modification, determination of appropriate glycemic targets, and initiation of pharmacologic therapy based on the initial HbA_{1C} at the time of diagnosis and presence of comorbidities. Current standards of care recommend initiating combination therapy for patients with an initial HbA_{1C} ≥1.5% above their glycemic target and combination injectable therapy for patients with an initial HbA_{1C} >10% and BG ≥300 mg/dL or for those who are markedly symptomatic. The selection of an agent should be based on the presence of ASCVD or high risk for ASCVD, heart failure, or CKD, the glucose-lowering need, and the impact on weight. When a patient has T2D and coexisting ASCVD or high risk for ASCVD, a GLP1 RA or SGLT2 inhibitor with proven benefit should be initiated. An SGLT2 inhibitor should be initiated in anyone with heart failure. An SGLT2 inhibitor should be initiated in anyone with CKD. A GLP1 RA should be considered if an SGLT2 inhibitor cannot be used. For patients where heart failure or CKD predominates, an SGLT2 inhibitor such as empagliflozin or canagliflozin should be added based on evidence that each agent has demonstrated reductions in HF and/or CKD progression. For patients without ASCVD, the choice of which agent to add to metformin should be based on patient-specific and drug-specific considerations, including efficacy, hypoglycemia risk, effect on weight, effect on ASCVD outcomes, renal effects, adverse effects, safety concerns, ease of use, and cost (Table 4.3). The response to therapy should be evaluated after 3 months. If the patient has not achieved his or her glycemic goals at that time, adherence should be assessed, and additional therapy should be considered.

The AACE guidelines recommend monotherapy for patients with an initial HbA_{1C} of <7.5%. Several medications are listed as potential options, in order of preferred use, with metformin highest on the list. Dual therapy is recommended for patients with an initial HbA_{1C} of ≥7.5% with metformin or other first-line agent plus an additional medication. Again, medications are suggested in a hierarchy of preference. For patients with an initial HbA_{1C} of >9%, the AACE guidelines suggest dual or triple therapy for those without symptoms and insulin with or without other agents for those with symptoms. The response to therapy should be evaluated after 3 months. If glycemic goals have not been achieved, adherence should be assessed, and therapy should be intensified. The hierarchy of drugs listed on the algorithm is based on the benefits and risks of each medication class. Minimizing the risk of hypoglycemia and weight gain are the priorities. It is also recognized that combination therapy is usually required and should involve drugs with complementary mechanisms of action.

Both the ADA and AACE recommendations are sequential in their approach. Some emerging research and commentaries are recognizing the limitations of this sequential approach, and some have even referred to it as a “treat to fail” approach. An alternative strategy is using early combination therapy that targets multiple pathophysiologic defects to quickly achieve and then maintain glycemic control for a longer period and to possibly salvage existing beta cell function. This approach is not currently recommended by major clinical guidelines but is an area that is under investigation.

20. What is the evidence supporting the use of specific agents in T2D patients with ASCVD?

In 2008, the FDA set a requirement that all new drugs developed and studied for the treatment of T2D must undergo CV safety testing. Subsequent trials have uniformly included participants with existing CVD or at high risk for CVD and studied a three-point MACE endpoint, including a composite of CV death, nonfatal MI, and nonfatal stroke. In these CVOTs, liraglutide, dulaglutide, subcutaneous semaglutide, empagliflozin, and canagliflozin have been reported to have beneficial effects on CV outcomes, as demonstrated in the LEADER (liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results), REWIND (researching cardiovascular events with a weekly incretin in diabetes), SUSTAIN-6 (trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes), EMPA-REG OUTCOME (empagliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients), and CANVAS (canagliflozin cardiovascular assessment study) studies, respectively.

TABLE 4.3 Drug-Specific and Patient Factors to Consider When Selecting Common Drug Therapy for TD2

	EFFICACY	HYPOGLYCEMIA RISK	EFFECT ON WEIGHT	ASCVD EFFECTS	PROGRESSION OF CKD EFFECTS	COST	ORAL/SC	ADVERSE EFFECTS AND SAFETY
Metformin	High	No	Neutral	Potential benefit	Neutral	Low	Oral	GI (diarrhea), B_{12} deficiency
SUs	High	Yes	Gain	Neutral	Neutral	Low	Oral	Hypoglycemia, weight gain
TZDs	High	No	Gain	Potential benefit (pioglitazone)	Neutral	Low	Oral	Edema, weight gain, risk of heart failure, bone fractures, bladder cancer
DPP4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral	High	Oral	Risk of heart failure, pancreatitis, joint pain
SGLT2 inhibitors	Intermediate	No	Loss	Benefit[a] ASCVD Heart Failure	Benefit[b]	High	Oral	GU infections, risk of volume depletion, hypotension, risk of amputations, bone fractures (canagliflozin), risk of DKA
GLP1 RAs	High	No	Loss	Benefit[c]	Benefit[d]	High	SC	GI (nausea, vomiting), injection site reactions, risk of thyroid C-cell tumors, pancreatitis, cholelithiasis
Basal Insulin	High	Yes	Gain	Neutral	Neutral	High	SC	Hypoglycemia, weight gain, Injection site reactions

[a] Empagliflozin, canagliflozin.

[b] Empagliflozin, canagliflozin, dapagliflozin, ertugliflozin

[c] Liraglutide, dulaglutide, subcutaneous semaglutide

[d] Semaglutide (primary outcome evidence), dulaglutide, liraglutide (secondary outcome evidence)

ASCVD, Atherosclerotic cardiovascular disease; *CKD*, chronic kidney disease; *DKA*, diabetic ketoacidosis; *DPP*, dipeptidyl peptidase; *GI*, gastrointestinal; *GLP*, glucagon-like peptide; *GU*, genitourinary; *RA*, receptor agonist; *SC*, subcutaneous; *SGLT*, sodium-glucose cotransporter; *SU*, sulfonylurea; *TZD*, thiazolidinedione; *TD2*, type 2 diabetes.

21. How should insulin therapy be initiated and titrated?

Basal insulin therapy should be initiated at a low dose (10 units or 0.1–0.2 units/kg) subcutaneously daily for safety and then titrated up by 10–15% (or 2–4 units) once or twice a week until the patient reaches the FPG target or a basal insulin dose of 0.5 units/kg is reached. On average, people with T2D treated with insulin glargine U-100 have a daily insulin dose of around 45 units. There are several available dose titration algorithms that can achieve optimal basal insulin doses, including the 3-0-3 method (if the 3-day FPG average is above goal, increase by 3 units; if at goal, no change; if below goal, decrease by 3 units). If a patient experiences hypoglycemia, the basal insulin dose should be reduced by 10–20% or 4 units. Doses of insulin glargine U-300 and insulin degludec should not be adjusted more frequently than every 3–4 days because of their longer half-lives. Patients should be educated upfront about how to titrate the dose as well as the anticipated final insulin dose. If patients are unable or unwilling to self-titrate, close follow-up is needed to ensure timely and effective insulin dosing.

22. When and how should insulin therapy be intensified?

If a patient does not reach his or her HbA_{1C} goal despite adequately titrated basal insulin, insulin therapy can be intensified by adding an injection of rapid-acting insulin before the largest meal or changing to premixed insulin twice daily (before the morning and evening meals). When implementing the former, a dose of 4 units should be given before the largest meal. When implementing the latter, the current basal dose should be divided as two-thirds in the morning (AM) and one-third in the evening (PM), or one-half (AM) and one-half (PM). In either case, the dose can be titrated up by 1–2 units or 10–15% once or twice a week until BG targets are achieved. If hypoglycemia occurs, the dose should be decreased by 10–20% or 2–4 units (similar to basal insulin).

In the event that the HbA_{1C} goal is not achieved with either strategy, rapid-acting insulin can be given at the two largest meals or at all three meals each day or the premixed insulin can be administered three times daily (breakfast, lunch, and dinner) by using the same titration strategy as described above.

Another option to intensify insulin therapy is to add a GLP1 RA to the basal insulin. This combination offers many potential benefits, including the provision of complementary mechanisms and effects on the glucose profile. GLP1 RAs complement basal insulin because they target PPG (short-acting GLP1 RAs) or PPG and FPG (long-acting GLP1 RAs). The combination is also effective at any stage of the disease process. Combination therapy may also potentially lower the risk of adverse effects. Basal insulin causes hypoglycemia and weight gain. GLP1 RAs do not cause hypoglycemia and lead to weight loss but do cause GI–related side effects. Combining the two classes may allow patients to achieve glycemic control with lower doses of both agents, potentially reducing the risk of adverse effects. Finally, the combination offers a potentially safer and easier option compared with adding rapid-acting insulin. The addition of a GLP1 RA to basal insulin does not require additional glucose monitoring or carbohydrate counting and carries a lower hypoglycemic risk compared with basal-bolus insulin therapy.

23. What is overbasalization?

Overbasalization is a term used to describe the continued use of escalating doses of basal insulin to target FPG, with no improvement in PPG or HbA_{1C}. The total daily insulin requirement in most patients with T2D is approximately 1 unit/kg/day and in more insulin-resistant patients is approximately 1.5 units/kg/day; the total daily dose (TDD) should be divided as 50% basal insulin and 50% rapid-acting insulin with meals. When this 50/50 guideline is violated by continuing to increase the basal insulin dose, overbasalization occurs. Overbasalization has the potential to alter the PK of basal insulin, leading to peaks and hypoglycemia, especially when patients miss or delay meals.

Overbasalization often occurs because of the desire to keep the insulin regimen simple and not prescribe multiple daily injections. However, many patients need medication (e.g., rapid-acting insulin) to cover their postprandial glucose excursions. Continually increasing their basal insulin dose will not correct a prandial defect in their glucose profile and will greatly increase the risk of hypoglycemia. Overbasalization can be avoided by not continuing the uptitration of basal insulin once the FPG is in the target range or the total basal dose is 0.5 units/kg/day; at this point, it is safer and more effective to add a strategy that will reduce PPG levels, such as meal-time rapid-acting insulin, a GLP1 RA, or an SGLT2 inhibitor.

24. When should glucose monitoring be done in T2D?

Blood glucose monitoring (BGM) using a glucometer or continuous glucose monitoring (CGM) is necessary for patients with T1D on intensive insulin regimens. The role of BGM and CGM in patients with T2D is less clear. Glucose monitoring alone does not improve glycemic control. It is only effective if the results are used to modify management strategies. However, BGM or CGM is appropriate in certain clinical situations. BGM (or CGM) should be prescribed for anyone who is taking a medication that increases the risk of hypoglycemia (insulin, sulfonylurea, meglitinide) so that testing can occur if hypoglycemia is suspected. If a patient is prescribed basal insulin, morning fasting glucose levels are required for basal insulin dose titration. If meal-time rapid-acting insulin is added, glucose monitoring before and after meals is necessary for titration of meal-time bolus doses. For all patients with T2D, BGM or CGM may be helpful to guide treatment decisions or lifestyle modification. However, clinical evidence is mixed about whether routine BGM or CGM improves HbA_{1C} in patients who are taking noninsulin medications only. The potential benefits must be weighed against the burden and cost of testing, and an individualized approach is recommended.

25. Which medications should not be used (or require dose adjustments) in patients with CKD?

Metformin may be used in patients with an eGFR ≥30 mL/min/1.73 m^2; however, it is not recommended that metformin be initiated in a patient with a baseline eGFR between 30 and 45 mL/min/1.73 m^2. When a patient's eGFR falls below 45 mL/min/1.73 m^2, continued use of metformin should be discussed. If continued, a half-maximal dose (1000 mg daily) should be considered.

Although no specific renal dose adjustment recommendations exist for glyburide, its use in patients with impaired renal function should be minimized because of its renal metabolism, accumulation of active metabolites, and the resulting risk of hypoglycemia; glipizide is a better choice if a sulfonylurea is used in this situation. The doses of DPP4 inhibitors alogliptin, saxagliptin, and sitagliptin need to be adjusted for patients with renal dysfunction; linagliptin is the only DPP4 inhibitor that does not require renal dysfunction dose adjustments. These agents may be useful in patients with renal dysfunction–related contraindications to metformin. Because of their action in the kidney, SGLT2 inhibitors are less effective in patients with renal impairment. Renal dose restrictions vary between products (see Table 4.2). While empagliflozin no longer has any restrictions for use in patients with CKD, the other agents have varying eGFR limits where the agent should not be initiated (dapagliflozin <25, canagliflozin <30, ertugliflozin <45, and bexagliflozin <30 mL/min/1.73 m^2).

Renal function of patients receiving exenatide twice daily with a creatinine clearance (CrCl) of 30–50 mL/min should be carefully monitored when increasing from 5–10-mcg doses; exenatide should not be used in patients with a CrCl <30 mL/min. There is limited experience in the use of liraglutide or dulaglutide in patients with severe renal impairment (CrCl 15–29 mL/min). Patients should not receive lixisenatide with a CrCl <15 mL/min. The prescribing information for dulaglutide and semaglutide does not include specific renal dose adjustment recommendations.

26. Which diabetes medication classes should not be used in combination?

Because of their overlapping mechanisms of action, GLP1 RAs and DPP4 inhibitors should not be used in combination. Both work by enhancing circulating GLP1 activity and are not likely to demonstrate increased efficacy when used in combination.

Although GLP1 RAs can be used in combination with insulin, the doses of insulin may need to be reduced when a GLP1 RA is added. If a GLP1 RA is initiated in a patient who is taking basal insulin and who has an A1C <8%, consider decreasing the dose of basal insulin by 20%. If a GLP1 RA is initiated in a patient taking rapid-acting insulin and who has an A1C <8%, consider decreasing the dose of rapid-acting insulin by 50%. Close monitoring is recommended and further adjustments may be necessary as the GLP1 RA achieves steady-state or as the dose is increased. Similarly, sulfonylurea doses should be lowered or discontinued when starting a GLP1 RA.

Other combinations that should not be used in combination include sulfonylureas, meglitinides, and rapid-acting insulins (in any combination) because of their overlapping mechanisms of action and the increased risk of hypoglycemia.

27. What is clinical inertia in diabetes management?

In diabetes care, clinical inertia is defined as the failure to establish appropriate glycemic targets and to escalate oral or injectable treatment to achieve these glycemic goals. Clinical inertia has a negative impact on patient care, including the development of preventable complications and excess direct and indirect health care costs. Contributing factors to clinical inertia include hesitation to start and optimize drug therapy early in the course of the disease, fear of side effects, and lack of provider support to properly monitor and titrate medications. Despite the development and availability of many new anti-hyperglycemic medications, only 50% of patients with diabetes achieve an HbA_{1C} goal of <7%. This failure to achieve glycemic targets is multifactorial, one potential reason being clinical inertia. Clinicians should appreciate the high rates of clinical inertia in T2D and consistently address glycemic control in their patients with T2D to avoid this inertia.

28. Can T2D be prevented or delayed?

Several studies have evaluated whether T2D could be prevented or delayed in individuals at high risk. The most notable of these is the diabetes prevention program (DPP). The DPP was a prospective, randomized trial evaluating the impact of intensive lifestyle intervention versus metformin versus placebo on the progression to diabetes diagnosis in patients with prediabetes. The intensive lifestyle intervention arm focused on achieving and maintaining 7% weight loss and 150 minutes of physical activity per week. This intervention was administered through a 16-session structured core curriculum followed by a maintenance program. The curriculum included sections on lowering calories, increasing physical activity, self-monitoring, healthy lifestyle behaviors, and psychological and social challenges. Results demonstrated that lifestyle intervention reduced the incidence of T2D by 58% over 3 years. Long-term follow-up in the study has shown sustained effects. Metformin reduced the incidence of T2D by 31% and, thus, was about half as effective as lifestyle modifications. Metformin, however, was as effective as lifestyle modifications in patients with a body mass index (BMI) ≥35 kg/m^2 and women with prior gestational diabetes. Metformin was not effective in patients over the age of 60 years. Clinical studies have also demonstrated the potentially beneficial effects of other pharmacologic interventions. TZDs, alpha-glucosidase inhibitors, GLP1 RAs, and orlistat have all decreased incident T2D in individuals with prediabetes, although none of these agents is FDA-approved specifically for diabetes prevention.

Therefore, the current ADA standards of care recommend that patients with prediabetes be referred to an intensive behavioral lifestyle intervention program modeled on the DPP to achieve and maintain 7% weight loss and increase moderate-intensity physical activity to at least 150 minutes per week. Metformin has the strongest efficacy and long-term safety evidence for diabetes prevention. In addition, cost, adverse effects, and durability should also be considered. Therefore, the ADA's recommendation for pharmacologic intervention to prevent or delay diabetes is limited to metformin. Specifically, the ADA suggests that metformin therapy should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those <60 years of age, and women with prior gestational diabetes.

KEY POINTS

- A glycosylated hemoglobin (HbA_{1C}) target should be established for each patient with T2D. A target HbA_{1C} of <7% is reasonable for most patients but should be individualized. A more stringent HbA_{1C} target may be appropriate for young, otherwise healthy patients with newly diagnosed T2D. A less stringent HbA_{1C} target may be appropriate for older patients with short life expectancies and serious comorbidities.
- The most common side effect of metformin is diarrhea. This side effect is usually transient and can be minimized by starting at a low dose and titrating up the dose slowly, taking the medication with food, and using an ER formulation.
- Major lifestyle modifications for T2D include weight loss (if overweight or obese) with an initial goal of 5% weight reduction, increased physical activity (at least 150 minutes per week of moderate to vigorous intensity exercise), and carbohydrate counting. Weight loss should focus on calorie restriction rather than macronutrient content. Healthy eating strategies, such as decreasing added sugars and solid fats, reducing portions, eating more vegetables, and shifting to whole grains and lower-fat dairy choices, should be encouraged.

Continued

KEY POINTS—cont'd

- HbA$_{1C}$ levels should be checked after 3 months of therapy. If the target HbA$_{1C}$ has not been achieved, adherence should be assessed, and additional therapy should be considered. Once the HbA$_{1C}$ target has been achieved, HbA$_{1C}$ levels can be measured every 6 months.
- Medications for T2D include metformin, SGLT2 inhibitors, GLP1 RAs, GLP1/GIP receptor agonists, DPP4 inhibitors, TZDs, sulfonylureas, and basal insulin. The decision about which to add should depend on whether the patient has established or high risk for ASCVD, heart failure, or chronic kidney disease. Other medication characteristics, such as glycemic efficacy, risk of hypoglycemia, effect on weight, ease of use, mechanism of delivery, cost, and side effects, should also be considered.
- Currently, SGLT2 inhibitors and some GLP1 RAs have positive CVOT data in patients with T2D and established ASCVD or high risk. In these patients, T2D therapy should begin with lifestyle modifications and initiation of an SGLT2 inhibitor or GLP1 RA with demonstrated benefit to reduce the risk of major adverse cardiovascular events. SGLT2 inhibitors have positive outcome data in patients with heart failure and chronic kidney disease and should be initiated in patients with T2D and these comorbidities. GLP1 RAs should be considered as an alternative therapy for patients with T2D and CKD when an SGLT2 inhibitor cannot be used or when additional therapy is needed.
- Basal insulin is an option in patients who have a markedly elevated HbA$_{1C}$ ($\geq$10%) or those who cannot achieve glycemic targets despite the use of other preferred medications. Basal insulin should be initiated at a dose of 10 units (or 0.1–0.2 units/kg) once daily and titrated up to glycemic targets. If FPG is controlled on basal insulin but the HbA$_{1C}$ is not at goal, therapy should be intensified with the addition of either a GLP1 RA or meal-time rapid-acting insulin.
- Intensive lifestyle modifications and metformin have both been proven to prevent or delay the onset of T2D in patients with prediabetes; lifestyle modification is about twice as effective as metformin. Lifestyle modification should focus on 7% weight loss and 150 minutes of moderate-intensity exercise per week. Metformin can be considered in addition to lifestyle modification, especially in those with a BMI $\geq$35 kg/m^2, those <60 years of age, and women with prior gestational diabetes.

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CHAPTER 5

Diabetes Technology: Continuous Glucose Monitoring and Insulin Pumps

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1. What is a continuous glucose monitor (CGM)?

A continuous glucose monitor (CGM) consists of a sensor, transmitter, and receiver. The sensor is inserted under the skin and measures interstitial glucose continuously (every 1–5 minutes). The transmitter sends glucose values to a receiver (monitor, cell phone, watch, insulin pump). The receiver displays the glucose values in real time and shows trend arrows that inform the user about the direction and magnitude of recent glucose level changes.

2. What is the difference between a personal CGM and a professional CGM?

Personal CGM devices are prescribed by providers and owned by users. They can be worn daily or intermittently. They display real-time glucose values and have audible or vibratory alarms to alert the user when glucose values are high or low or will soon be high or low. Professional CGM devices are owned by providers and are loaned to users for periods of 1–2 weeks. The devices are then returned to the office, where CGM data is downloaded and analyzed.

3. How accurate are CGM devices compared to blood glucose measurements?

CGM measures interstitial fluid glucose and not blood glucose (BG). When BG levels are stable, interstitial glucose values are usually very close to BG levels. When BG levels are changing, interstitial glucose values lag by up to 15–30 minutes and thus will give lower readings when BG levels are rising and higher readings when BG values are falling. Current CGM has a Mean Absolute Relative Difference (MARD) of ≤10%, which means that the sensors report glucose levels that are within 10% of a gold standard lab BG measurement.

4. What are the features of personal CGM devices and how do they differ?

Table 5.1 lists the currently (2024, 3rd Quarter) available personal CGM devices with their warm-up times, wear times, need for calibration, and current approval for integration with insulin pumps. FDA approvals for pump integration are a rapidly changing field.

5. What is the ambulatory glucose profile (AGP)?

The AGP is generated from the CGM download (usually for a 2-week period). It consists of a glucose management indicator (GMI), which is an estimate of the A1c equivalent for that 2-week period; the overall average glucose value; the percent of the time in range (TIR) at various levels; glucose variability (coefficient of variation and/or standard deviation); and active CGM wear time. If the active CGM wear time is <90%, the CGM download data must be analyzed cautiously, since the data will likely not represent a full picture of the individual's glycemia during that 2-week period. A coefficient of variation >36% is consistent with marked variability.

A suggested system for recording the AGP in a person's chart is shown below.

Time (%) CGM active: ___%
GMI: ___%
Average BG: ___ mg/dL
TIR:
TIR >250 mg/dL: ___%
TIR >180 mg/dL: ___%
TIR 70–180 mg/dL: ___%
TIR <70 mg/dL: ___%
TIR <54 mg/dL: ___%
Coefficient of variation: ___%
  Standard deviation: ___ mg/dL

TABLE 5.1 Personal Continuous Glucose Monitors (3rd Quarter, 2024)

CGM	NEED TO CALIBRATE	WARM-UP TIME	SENSOR WEAR TIME	PUMP INTEGRATION
Dexcom G6	No	2 hours	10 days	T-Slim X2[*], Mobi[*], Omnipod 5[**], iLet[#]
Dexcom G7	No	30 min.	10 days	T-Slim X2[*], Mobi[*], Omnipod 5[**], iLet[#]
Dexcom Stelo	No	30 min.	15 days	No
Guardian 3	2x/day	2 hours	7 days	670G[##], 770G[##], 780G[##]
Guardian 4	No	2 hours	7 days	780G[##]
Libre 2	No	1 hour	14 days	No
Libre 2 Plus	No	1 hour	15 days	T-Slim X2[*]
Libre 3	No	1 hour	14 days	No
Eversense E3	2x/day	1–24 hours	6 months	No

[*] Tandem
[**] Insulet
[#] Beta Bionics
[##] Medtronic
Note: FDA approval for CGM integration with insulin pumps changes continuously.
CGM, continuous glucose monitor

TABLE 5.2 CGM TIR Targets in Nonpregnant Adults (2021)

	Older/High-Risk	
	TYPE 1 + TYPE 2	**TYPE 1 + TYPE 2**
Glucose	Target TIR	Target TIR
>250 mg/dL	<5%	<10%
>180 mg/dL	<25%	<50%
70–180 mg/dL	>70%	>50%
<70 mg/dL	<4%	<1%
<54 mg/dL	<1%	0%

TIR, time in range

6. What are the TIR targets for people using personal CGM?

See Table 5.2

7. How are CGM trend arrows used to help with optimal insulin dosing decisions?

Trend arrows show the direction and magnitude of glucose changes. The changes are depicted by arrows or dials with arrows that indicate whether the current glucose will likely remain stable or will be increasing or decreasing, and at what rate, over the next 30–60 minutes. This information helps users or integrated systems make appropriate insulin dosing adjustments.

8. Does CGM improve glycemic control in people with type 1 diabetes?

Multiple studies in people with type 1 diabetes, treated with multiple daily insulin injections or insulin pumps, have demonstrated that CGM use significantly reduces A1c, increases glucose time in target range, reduces time in hypoglycemia, improves hypoglycemia awareness in those with hypoglycemia unawareness, reduces hospitalizations for hyperglycemic and hypoglycemic emergencies, and improves quality of life.

9. Does CGM improve glycemic control in people with type 2 diabetes?

Personal CGM in people with type 2 diabetes who are taking multiple daily insulin injections has been reported to significantly reduce A1c levels. Professional CGM done intermittently (3-month intervals) in people with type 2 diabetes in general practices has also been shown to reduce A1c and to improve glucose time in the target range.

10. Can CGM be used in hospitalized patients including those in intensive care?

CGM has also been shown to be accurate and useful for monitoring glucose levels in hospitalized patients both in noncritical and critical care. Studies have generally demonstrated a reduction in the rate of hypoglycemia, and some demonstrate improved glycemic control.

11. What is an insulin pump?

Insulin pumps deliver insulin continuously through a subcutaneous site. They consist of an insulin reservoir, a pumping mechanism, and an infusion set. The reservoir holds a 2–3 days' insulin supply; it is filled with insulin drawn from a vial into a syringe and injected into the reservoir. The infusion set is either tubing that terminates in a plastic cannula that is inserted under the skin or a plastic cannula that extends directly from the pump into the skin without external tubing. A small needle inside the cannula is used to insert the cannula through the skin and is then withdrawn to leave the hollow cannula under the skin.

12. How does an insulin pump deliver insulin?

Insulin pumps deliver both basal insulin and bolus insulin. Basal insulin is a continuous 24-hour infusion that controls hepatic glucose production overnight and between meals. Bolus insulin is an acute dose to cover a meal, to correct a high glucose level, or both. Bolus doses have two components: a nutritional dose and a correction dose. The nutritional dose is the insulin required to cover a meal the person is about to eat. The correction dose is the additional insulin that is added to the nutritional dose if the premeal BG is elevated; correction boluses may also be taken alone between meals to correct high glucose values.

13. What type of insulin is used in insulin pumps?

Rapid-acting insulin analogs are used in insulin pumps. Occasionally, regular human insulin is used, and people with very high insulin requirements (>200 units daily) may use U500 regular insulin in their pumps. However, regular insulin and U500 regular insulin provide less effective coverage of the rapid glucose rise that occurs after meals and are not FDA-approved to be used in insulin pumps.

14. What are the benefits of using insulin pump therapy?

The basal insulin infusion rate can be varied throughout the day to match a person's activities and individual glucose patterns. Pumps also have bolus calculators that compute exact bolus insulin doses based on a meal's carbohydrate content, the current glucose level, and the carbohydrate to insulin (C:I) ratios and correction factors (CF) that are preprogrammed into the pump. Most pumps have an "insulin on board" feature that prevents excessive correction bolus doses by taking into account the remaining insulin effect from a previous bolus dose. Some pumps can also integrate with CGM (see below).

15. How do you estimate a person's initial C:I ratios and CF?

If a person does not already have an established C:I ratio and CF, the initial C:I ratio can be calculated by the following equation: C:I ratio = 500/TDD (TDD = total daily dose of insulin). Similarly, the CF can be calculated by the following equation: CF = 1650/TDD.

Some providers recommend different equations for these initial calculations, but we find these to be accurate in our clinic population in Colorado. However, these are only initial estimates; basal rates, C:I ratios, and CF must be modified by analyzing subsequent glucose profiles.

16. How do you determine initial basal rates and bolus dosing for insulin pump therapy?

Most people who are starting insulin pump therapy are already taking multiple daily insulin injections with both basal and bolus components. The current dose of injected basal (long-acting) insulin can be used to calculate the initial insulin pump basal rates. If the A1c is less ≤8.0%, the current injected basal dose should be reduced by 10–20%, and this value is then divided by 24 to determine the initial hourly basal infusion rate. If the A1c is >8% and the person is not having frequent hypoglycemia, the current full injected basal dose can be used and similarly be divided by 24 to determine the initial hourly basal infusion rate. Most people who transition to insulin pump therapy are already using a C:I ratio and a CF for their injections; if these ratios are working properly, the same ratios can be used with the insulin pump.

17. Let's look at an example of calculating initial basal rates, the C:I ratio, and the CF.

A 22-year-old woman with type 1 diabetes mellitus for 3 years has decided to transition to insulin pump therapy. Her A1c is 8.9% and she has hypoglycemia about once a month. Her current dose of injected basal insulin is 20 units daily. Her bolus insulin consists of 6 units for breakfast, 7 units for lunch, 7 units for dinner, and a correction factor of 50:1 with a target of 100 mg/dL. You have her attend carbohydrate counting classes and she does well.

Her initial insulin pump settings could be calculated as follows:
TDD = 20 + 6 + 7 + 7 = 40 total insulin units/day
Basal rates: 20 units / 24 hours = 0.8 units/hour
Bolus doses: C:I Ratio (500/TDD) = 500/40 = 13:1; CF (1650/TDD) = 1650/40 = 40:1

18. How are basal insulin rates evaluated in nonintegrated insulin pumps?

Basal insulin rates should maintain stable BG levels with changes of ≤30 mg/dL overnight and during intervals when no food or bolus doses are taken. For example, if bedtime BG is in the 110–150 mg/dL range and no snacks or boluses are taken, the next AM fasting BG (FBG) should be in the 80–130 mg/dL range.

19. How are the bolus insulin doses evaluated in nonintegrated insulin pumps?

If the C:I ratio is correct and carbohydrate counting is accurate, BG excursions from premeal to 2 hours postmeal should be about 30–50 mg/dL. C:I ratio accuracy is best tested by eating a meal of known carbohydrate content and with <20 gm of fat, taking the calculated amount of premeal insulin, and then rechecking the BG level 2 hours after the meal; this test is valid only if a premeal correction dose is not needed. CF accuracy can be tested by determining if BG levels fall into the target range after nonmeal correction doses.

20. What can cause sudden deterioration of BG control on insulin pump therapy?

When unexplained hyperglycemia suddenly occurs, the following should be evaluated: dose timing and accuracy, infection, stress, medication changes, diet changes, physical activity changes, insertion site problems, infusion set issues (occlusion, kinking), and bad insulin. Individuals should also check for ketones and ensure adequate oral hydration. Injected correction doses may be temporarily needed.

21. What insulin pumps are currently available in the United States?

There are multiple brands of insulin pumps in the United States (3rd Quarter, 2024): Medtronic 670G, 770G, 780G; Tandem t:slim X2, Tandem Mobi; Insulet Omnipod Dash, Omnipod 5; Beta Bionics iLet, V-Go, Cequr, and Deka. Medtronic 670G-780G, Tandem t:slimX2 and Tandem Mobi, Insulet Omnipod Dash and Omnipod 5, Beta Bionics iLet and Deka are computer-controlled electronic pumps; V-Go and Cequr are mechanical pumps. Medtronic 670G-780G, Tandem t:slim X2, Tandem Mobi, Beta Bionics iLet and Deka pumps use hollow external tubing to connect to the insertion site. Insulet Omnipod Dash and Omnipod 5, V-Go, and Cequr connect to the insertion site from the underside of the pump with no external tubing. Medtronic 670G-780G, Tandem t:slim X2, Tandem Mobi, Insulet Omnipod 5, Beta Bionics iLet, and Deka can integrate with CGM for automated insulin delivery (AID) (see Table 5.3).

22. What is automated insulin delivery?

AID uses a control algorithm to integrate CGM data with insulin delivery by an insulin pump. The AID algorithm analyzes CGM data and automatically adjusts basal rates and correction doses to maintain BG levels within a target range. Current (3rd Quarter, 2024) AID systems are the Medtronic 670G/Guardian 3, 770G/Guardian 3, and 780G/Guardian 4; Tandem t:slim X2/

TABLE 5.3 Insulin Pumps Available in the United States (3rd Quarter, 2024)

INSULIN PUMP	EXTERNAL TUBING	RESERVOIR CAPACITY	CGM INTEGRATION
Beta Bionics iLet	Yes	180 units	Dexcom G6, G7
Medtronic 670G	Yes	300 units	Guardian 3
Medtronic 770G	Yes	300 units	Guardian 3
Medtronic 780G	Yes	300 units	Guardian 4
Tandem t:slim X2	Yes	300 units	Dexcom G6, G7, Libre 2 Plus
Tandem Mobi	Yes	200 units	Dexcom G6, G7
Insulet Omnipod 5	No	200 units	Dexcom G6, G7
Insulet Omnipod Dash	No	200 units	No
Accu-Chek Solo Tubeless	No	200 units	No
Cequr	No	1–4 days	No
V-Go	No	1 day	No

TABLE 5.4 Features of Medtronic (MiniMed) 780G With SmartGuard

Sensor: Guardian 4 (calibration may be requested but no routine calibration required) or Guardian 3 (calibration required every 12 hours; improved accuracy with calibration 3–4 times per day). Both: 7-day wear time.

Initialization: Program basal rates, C:I ratios*, CFs**, BG targets, and AIT***. SmartGuard can be activated after a 48-hour warm-up period which begins at midnight after the pump starts delivering insulin. The recommended initial AIT is 2–3 hours when using SmartGuard.

Basal Rate: Auto-adjusts every 5 minutes based on BG trends. Auto-basal (automated basal insulin) is calculated from total daily insulin. New basal rates with the algorithm are updated every midnight. Users cannot adjust basal rates.

Basal BG Target Options: 100 mg/dL, 110 mg/dL, or 120 mg/dL. Only one target can be set.

Correction Bolus: Auto-corrections can be given up to every 5 minutes when max basal is reached and BG >120 mg/dL. Can turn on or off. User can give manual correction boluses.

Correction BG Target: 120 mg/dL for both auto-corrections and manual corrections.

Meal Bolus: User must manually enter the meal carb amount. Programmed C:I will be used. If using the Guardian sensor and SmartGuard, sensor BG will autopopulate into the bolus calculator; the calculated bolus may be adjusted based on BG and trend.

Bolus Override Option: Not when using SmartGuard.

Extended Bolus Option: Square wave and dual wave options are not available when using SmartGuard.

Settings That Can Be Adjusted: BG target for auto-basal, C:I ratios, AIT.

Special Features: Temp target of 150 mg/dL for exercise/physical activity (will not receive autocorrections).

Tubing: Yes

**C:I* ratio, carbohydrate to insulin ratio.
***CF,* Correction factor. Also known as *ISF*, insulin sensitivity factor.
****AIT*, active insulin time.

Dexcom G6/G7, Tandem t:slim X2/Libre 2 Plus, Tandem Mobi/DexcomG6/G7; Insulet Omnipod 5/Dexcom G6/G7, and Beta Bionics iLet/Dexcom G6/G7. The Medtronic 670G-780G, Tandem t:slim X2, Tandem Mobi, and Insulet Omnipod 5 systems are hybrid closed-loop systems that adjust basal rates and correction doses but do not deliver meal-time boluses; accurate carbohydrate counting and an appropriate C:I ratio are still required for meal coverage. The Beta Bionics iLet also requires meal announcements but instead of carbohydrate counting, allows for minimal input after the user programs in the usual meal size.

23. Describe the features of the various AID systems.

Tables 5.4–5.7 compare and contrast the current AID systems.

TABLE 5.5 Features of Tandem t:slim X2 and Tandem Mobi With Control IQ

Sensor: Dexcom G6 or G7 (factory calibrated, 10-day sensor wear time), or Libre 2 Plus (factory calibrated, 15-day sensor wear time).
Initialization: Program basal rates, C:I ratios[*], and CFs[**]. Turn on Control IQ (must wear Dexcom G7 sensor and transmitter to use Control IQ). AIT[***] fixed at 5 hours in Control IQ.
Basal Rate: Auto-adjusts based on a 30-minute prediction of BG levels. The pump will deliver a programmed basal rate when the predicted BG value is within the target range.
Basal BG Target Options: The control IQ algorithm targets BG 112.5–160 mg/dL; cannot be adjusted when using Control IQ.
Correction Bolus: Automatic corrections (auto corrections) will be given when BG is predicted to be ≥180 mg/dL in 30 minutes and Control IQ technology is increasing insulin delivery or at maximum insulin delivery. Auto corrections are 60% of a calculated correction bolus (based on CF and current BG) and can be delivered up to once per hour. User can give manual correction boluses.
Correction BG Target: 110 mg/dL
Meal Bolus: User must manually enter the meal carb amount. Programmed C:I will be used. Bolus calculation will be reduced if BG is below target.
Bolus Override Option: Yes
Extended Bolus Option: Yes, up to 2 hours.
Settings That Can Be Adjusted: Basal rates, C:I ratio(s), CF(s)
Special Features: Exercise activity (BG target 140–160 mg/dL; will still get autocorrections when BG is predicted to be ≥180 mg/dL in 30 minutes); Sleep activity (BG target 112.5–120 mg/dL; no autocorrections; sleep schedule can be set or can enter sleep activity manually).
Tubing: Yes

[*] *C:I* ratio, carbohydrate to insulin ratio.
[**] *CF*, Correction factor. Also known as *ISF*, insulin sensitivity factor.
[***] *AIT*, active insulin time.

TABLE 5.6 Features of Insulet Omnipod 5 With Automated Mode

Sensor: Dexcom G6 or G7 (factory-calibrated, 10-day [G6] or 10.5-day [G7] sensor wear time), “correct above,” and AIT[***]. Switch to automated mode.
Basal Rate: Auto-adjusts every 5 min based on a 60-min prediction of BG level. Automated basal insulin (adaptive basal rate) is calculated from total daily insulin and updated with each pod change. User cannot adjust basal rates in automated mode.
Basal BG Target Options: 110 mg/dL, 120 mg/dL, 130 mg/dL, 140 mg/dL, 150 mg/dL. Up to eight different targets can be set per 24 hours.
Correction Bolus: No automated boluses. User can give manual correction boluses. Option to turn “reverse correction” on which may reduce meal bolus if BG is below target.
Correction BG Target: 110 mg/dL, 120 mg/dL, 130 mg/dL, 140 mg/dL, 150 mg/dL. “Correct above” settings are programmed upon initialization.
Meal Bolus: User must manually enter the meal carb amount. Programmed C:I will be used. Option to turn “reverse correction” to reduce meal bolus if BG is below target.
Bolus Override Option: Yes
Extended Bolus Option: Not available in automated mode.
Settings That Can Be Adjusted: C:I ratio, CF, BG target, correct above, AIT.
Special Features: Activity feature (BG target 150 mg/dL, 50% decrease in adaptive basal rate).
Tubing: No

[*] *C:I* ratio, carbohydrate to insulin ratio.
[**] *CF*, Correction factor. Also known as *ISF*, insulin sensitivity factor.
[***] *AIT*, active insulin time.

24. What is a bi-hormonal pump?

A bi-hormonal pump delivers insulin to lower BG and glucagon to acutely raise low BG levels as needed. Currently (3rd Quarter, 2024) available pumps are uni-hormonal (insulin only). They can shut off when hypoglycemia occurs, but insulin already delivered is still active and prevents rapid resolution of hypoglycemia. Bi-hormonal pumps solve this problem by shutting off insulin and giving a glucagon bolus to rapidly correct hypoglycemia. Bi-hormonal systems are in development but are not yet FDA-approved (as of this writing).

TABLE 5.7 Features of Beta Bionics iLet Bionic Pancreas

Sensor: Dexcom G6 or G7 (factory calibrated, 10-day [G6] or 10.5-day [G7] sensor wear time). If no active G6 sensor, iLet will enter “BG-run Mode” and request BG every 4 hours to continue insulin delivery. All insulin delivery will stop after 72 hours with no active G6 sensor. Dexcom G7 may have been approved for use with this system after this chapter was written.
Initialization: Enter body weight. There are no pump settings to enter.
Basal Rate: Auto-adjusts every 5 min based on BG profile over the previous 24 hours, current BG, and BG trend.
Basal BG Target Options: Usual (120 mg/dL), lower (110 mg/dL), higher (130 mg/dL).
Correction Bolus: Automated every 5 min based on current BG, BG trend, insulin on board, and adapted aggressiveness.
Correction BG Target: Usual (120 mg/dL), lower (110 mg/dL), higher (130 mg/dL).
Meal Bolus: Meal announcement “usual for me,” “more (around 50% more CHO compared to usual),” “less” (around 50% less CHO compared to usual) based on carbohydrates in the meal (not total size of the meal) and what the user considers to be breakfast, lunch, or dinner. When the meal is announced, the pump will provide 75% of the overall insulin needed for that meal type. Meal doses are adapted over time.
Bolus Override Option: No
Extended Bolus Option: No
Settings That Can Be Adjusted: BG targets (usual, lower, higher). Updated body weight if it changes by more than 15%.
Special Features: Sleep target (can be set for any start and end time)
Tubing: Yes

25. What is open-source AID or do-it-yourself (DIY) technology?

Open-source AID, also known as DIY technology (or looping) began in 2013 when the #WeAreNotWaiting community developed their own algorithm for AID using commercially available pumps and CGM and made the code available online. Two systems that are currently in wide use are the AndroidAPS (Android device) and the Loop (iOS device). The Tidepool Loop open-source system was subsequently approved by the FDA. Two randomized controlled trials have demonstrated that glucose time in range using open-source AID was similar to or superior to a comparator commercial AID system. The Clears Twiist AID system was also approved in 2024 for use with the new Deka insulin pump, a compatible CGM sensor, and the Tidepool Loop algorithm.

26. What are Smart Pens?

The INPEN and Tempo are injection devices for rapid acting insulin that can be programmed with a C:I ratio for meals and a CF for high glucose levels. The carbohydrate content of an intended meal can be entered via a cell phone app, and the glucose value can be directly entered or uploaded from a compatible glucometer or CGM. The pen calculates correct bolus doses and records them along with glucose data. Glucose and insulin dose data from the devices can be downloaded prior to or during the next patient visit.

KEY POINTS

- CGM consists of (1) a sensor inserted under the skin to measure interstitial glucose every 5 minutes; (2) a transmitter that transmits glucose values; and (3) a receiver that displays glucose values in real time and shows trend arrows to inform the user about the direction and magnitude of glucose changes.
- Professional CGM devices are loaned by providers to users for 1–2 weeks at a time. Personal CGM devices are prescribed by providers and owned by users to be worn daily.
- CGM provides real-time interstitial glucose values, trend arrows, and alarms that alert for hypoglycemia, hyperglycemia, and predicted hypoglycemia/hyperglycemia.
- The AGP, generated by CGM consists of a GMI – 2-week A1c estimate; the average glucose value; the % TIR at various levels; glucose variability; and active CGM wear time.
- CGM has been demonstrated in people with type 1 and type 2 diabetes to improve glucose control, reduce hospitalizations for diabetic ketoacidosis and hypoglycemia, and improve quality of life.
- Insulin pumps consist of an insulin reservoir, a pumping mechanism, and an infusion set through which insulin is delivered continuously into a subcutaneous site. Rapid-acting insulin analogs are the most common type of insulin used in pumps.

KEY POINTS—cont'd

- Basal insulin infusion rates can be varied throughout the day to match a person's activities and individual glucose patterns.
- Bolus insulin has two components: a nutritional dose (to cover meals) and a correction dose (to reduce existing high BG levels).
- Insulin pumps have bolus calculators to accurately compute bolus insulin doses based on the user-estimated meal carbohydrate content, the current glucose level, and the programmed carbohydrate to insulin (C:I) ratios and correction factors.
- AID systems integrate CGM data to adjust insulin delivery by an insulin pump. Multiple systems with individualized features are available.

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CHAPTER 6

Carbohydrate Counting and Precise Insulin Dosing

Michael T. McDermott

1. Define and explain the carbohydrate-to-insulin ratio.

The carbohydrate-to-insulin ratio (C:I ratio) is an estimate of the grams of carbohydrate that will be covered by each 1 unit of insulin. A C:I ratio of X:1 means that 1 unit of insulin should be given for each X grams of carbohydrate to be consumed. The initial C:I ratio for each person is usually calculated as follows: 500/total daily dose (TDD) of insulin. The C:I ratio must then be evaluated and adjusted to achieve optimal preprandial to postprandial blood glucose (BG) excursions (optimal: 30–50 mg/dL rise from premeal to 2 hours postmeal).

2. How do you determine if the current C:I ratio is correct?

We test the accuracy of each person's C:I ratio with the following protocol:

A. Preparation for the test meal: consume something that is easily covered at the meal prior to the test meal, so that the glucose level immediately before the test meal is in the target range and does not require a correction dose. If glucose prior to the test meal is <70 mg/dL or >140 mg/dL, don't proceed with the test.
B. If the glucose just before the test meal is in the desired range (70–140 mg/dL), eat a meal that has a well-known carbohydrate content and less than 20 grams of fat.
C. Test your glucose level just before the test meal, take the insulin dose calculated from your C:I ratio, and recheck your glucose 2 hours after the test meal; calculate the pre and post glucose excursion. The glucose excursion from premeal to 2 hours postmeal should be about 30–50 mg/dL.
D. If the rise is >50 mg/dL, the C:I ratio should be strengthened; if the rise is <30 mg/dL, the C:I ratio should be weakened.

3. What is a high blood glucose correction factor (CF)?

A correction factor (CF) is an estimate of the BG drop expected for each 1 unit of insulin given when BG is elevated above the goal. A CF of N:1 means that 1 unit of insulin will drop the BG N mg/dL; therefore, a person will give 1 unit of insulin for every N mg/dL if the current BG level is above the BG target. We calculate an initial CF as 1650/TDD (some providers use 1800/TDD, 1700/TDD or 1500/TDD). The initial CF must then be evaluated and adjusted to achieve appropriate reductions of high BG to the target range by 4 hours after the dose is given.

4. How do you calculate and use the insulin bolus on board (BOB) and duration of insulin action (DIA) estimates?

Bolus on board (BOB) and insulin on board (IOB) are similar terms used to indicate how much insulin is still active after the last rapid-acting insulin bolus; we will use the term BOB here. Duration of insulin action (DIA) and active insulin time (AIT) are similar terms used to indicate how long an insulin bolus lasts for an individual; we will use the term DIA here. DIA is often approximately 4 hours, but some people consider their DIA to be shorter (approximately 3 hours) or longer (approximately 5 hours) based on their own experience.

To calculate the BOB, use the previous bolus dose and subtract from that the same dose multiplied by the time elapsed since that bolus was divided by the DIA. The formula is therefore: BOB = bolus – bolus × (elapsed time since bolus / DIA). Example: if a 6-unit bolus was taken 2 hours ago and the DIA is 4 hours, the BOB is 3 units (6 - 6 × [2/4] = 3). When a person plans to take a high BG correction dose, the BOB should be subtracted from the planned correction dose.

5. Do people who take basal bolus insulin need to do these calculations before every meal and correction dose?

People who administer insulin by multiple daily injections (MDI) should be very familiar with their C:I ratio and CF and use them to calculate every meal bolus and correction bolus. Insulin pumps automatically calculate the necessary insulin dose for the carbohydrate content, the correction dose, and the BOB and display the recommended dose of insulin. In either case, accurate carbohydrate counting is essential.

6. Explain what additional information is provided by a continuous glucose monitor.

A continuous glucose monitor (CGM) is a subcutaneous device that measures interstitial glucose every 3–5 minutes and displays it in real time or intermittently. A person sees the current glucose value along with a trend arrow to indicate the direction glucose is going (trend). CGM will be discussed in more depth in a subsequent chapter.

7. What basic carbohydrate counting skills should every patient with diabetes and their providers know?

Carbohydrate counting is usually taught by a certified diabetes education specialist (CDES). However, all providers involved in managing people with diabetes on insulin regimens should be familiar with the basics of carbohydrate counting. Table 6.1 is useful as an introduction to the basics of carbohydrate counting and for the practice cases presented later in this chapter.

TABLE 6.1 Carbohydrate Counting Basics

15 Gram (g) Carbohydrate Servings (60 kcal of Carbohydrate)
1 slice of bread = 15 g carbohydrate
1 small roll = 15 g carbohydrate
1 small potato (3 oz) = 15 g carbohydrate
½ cup of mashed potatoes = 15 g carbohydrate
½ cup of corn = 15 g carbohydrate
½ cup of peas = 15 g carbohydrate
⅓ cup of cooked rice = 15 g carbohydrate
⅓ cup of cooked pasta = 15 g carbohydrate
1 medium apple = 15 g carbohydrate
½ of a 6-inch banana = 15 g carbohydrate
2 Oreos = 15 g carbohydrate
2 × 2-inch unfrosted cake = 15 g carbohydrate
½ cup (4 oz) of fruit juice = 15 g carbohydrate
1.25 cup (10 oz) of milk = 15 g carbohydrate
1.5 cup (12 oz) regular beer or nonalcoholic beer = 15 g carbohydrate

30 Gram (g) Carbohydrate Servings (120 kcal of Carbohydrate)
1 medium potato (6 oz) = 30 g carbohydrate
1 cup of mashed potatoes = 30 g carbohydrate
1 cup of corn = 30 g carbohydrate
1 cup of peas = 30 g carbohydrate
⅔ cup of cooked rice = 30 g carbohydrate
⅔ cup of cooked pasta = 30 g carbohydrate
1 6-inch banana = 30 g carbohydrate
4 Oreos = 30 g carbohydrate
1 cup (8 oz) wine cooler = 30 g carbohydrate
1.5 cup (12 oz) microbrew beer = 30 g carbohydrate
½ cup (4 oz) margarita = 30 g carbohydrate
½ cup (4 oz) daiquiri = 30 g carbohydrate

45 Gram (g) Carbohydrate Servings (180 kcal of Carbohydrate)
1 cup of cooked rice = 45 g carbohydrate
1 cup of cooked pasta = 45 g carbohydrate
6 Oreos = 45 g carbohydrate

Other Gram (g) Carbohydrate Servings (1 g Carbohydrate = 4 kcal)
1 small corn tortilla = 10 g carbohydrate
1 cup (8 oz) milk = 12 g carbohydrate
1 can (12 oz) regular soda = 40 g carbohydrate
1 bottle (20 oz) regular soda = 75 g carbohydrate
1 teaspoon sugar (5 mL) = 4 g carbohydrate
1 tablespoon sugar (15 mL) = 12 g carbohydrate
1 teaspoon honey (5 mL) = 5 g carbohydrate
1 tablespoon honey (15 mL) = 15 g carbohydrate

8. Practice with carbohydrate counting and precise insulin dosing.

Let's work through some cases. Table 6.1 (above) lists the estimated carbohydrate contents for the common meals we will present. [C:I = carbohydrate-to-insulin ratio, CF = correction factor, BG = blood glucose]. Note: in these cases, people taking multiple daily insulin injections will round their insulin doses to the nearest whole digit, whereas those using insulin pump therapy can give fractional doses if needed.

CASE 1

Victor has type 1 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 32 units daily
Bolus Insulin: C:I ratio = 10:1, CF = 40:1, BG Target = 100 mg/dL
Premeal BG = 180 mg/dL
Planned Meal:
Ham sandwich
Medium apple
Oreo cookies - 2
Milk – 1 cup

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 2

Hayley has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 28 units daily
Bolus Insulin: C:I ratio = 12:1, CF = 45:1, BG Target = 100 mg/dL
Premeal BG = 235 mg/dL
Planned Meal:
Small corn tortilla
Cooked rice – ⅓ cup
Fruit juice – 1 cup
Banana – 6-inch

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 3

Chloe has type 1 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 18 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 50:1, BG Target = 120 mg/dL
Premeal BG = 220 mg/dL
Planned Meal:
Cooked pasta – 1 cup
Peas – ½ cup
Small roll
Wine cooler

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 4

Mac has type 2 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 36 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 25:1, BG Target = 100 mg/dL
Premeal BG = 175 mg/dL
Planned Meal:
Eggs, scrambled – 2
Toast – 2 slices
Honey – 1 teaspoon on each piece of toast
Fruit juice – 1 cup

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 5

Gene has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 32 units daily
Bolus Insulin: C:I ratio = 10:1, CF = 35:1, BG Target = 110 mg/dL
Premeal BG = 180 mg/dL
Planned Meal:
Beef – 6 oz
Baked potato – medium
Corn – ½ cup
Microbrew beer – one
Regular beer - one

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 6

Katy has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 22 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 50:1, BG Target = 120 mg/dL
Premeal BG = 195 mg/dL
Planned Meal:
Grilled cheese sandwich
Mashed potatoes – 1 cup
Banana – 6-inch
Regular soda – 12 oz

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 7

Emily has type 2 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 38 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 25:1, BG Target = 110 mg/dL
Premeal BG = 210 mg/dL
Planned Meal:
Eggs, fried – 2
Bacon – 2 slices

French toast – 2 slices
Banana, sliced – 3-inch
Powdered sugar – 1 teaspoon
Tea with honey - 1 teaspoon

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 8

Leonard has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 26 units daily
Bolus Insulin: C:I ratio = 12:1, CF = 40:1, BG Target = 100 mg/dL
Premeal BG = 200 mg/dL
Planned Meal:
Baked chicken – 2 pieces
Mashed potatoes – 1 cup
Peas – 1 cup
Milk – 1 cup

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 9

Sonja has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 24 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 60:1, BG Target = 110 mg/dL
Premeal BG = 200 mg/dL
Planned Meal (Friday Night):
Beef – 8 oz
Corn tortillas, small – 3
Rice – $\frac{2}{3}$ cup
Margarita – 8 oz

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

CASE 10

Henry has type 2 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 42 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 30:1, BG Target = 120 mg/dL
Presnack BG = 210 mg/dL (4 hours after lunch)
Planned Snack:
Oreo cookies – 4
Milk – 1 cup

1. How many grams of carbohydrate does this meal contain? _______ g
2. How much insulin will be needed to cover the carbohydrates? _______ units
3. How much insulin will be needed to correct the premeal glucose? _______ units
4. What total dose of insulin should be taken? _______ units

Here are the answers to the 10 cases above. Yours may be slightly different if you disagree with the carbohydrate contents listed here. This is OK as long as you follow sound principles of carbohydrate counting and do accurate math.

CASE 1 Answers

Victor has type 1 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 32 units daily
Bolus Insulin: C:I ratio = 10:1, CF = 40:1, BG Target = 100 mg/dL
Premeal BG = 180 mg/dL
Planned Meal:
Ham sandwich (30 g)
Medium apple (15 g)
Oreo cookies – 2 (15 g)
Milk – 1 cup (12 g)

1. How many grams of carbohydrate does this meal contain? 72 g
2. How much insulin will be needed to cover the carbohydrates? 7 units
3. How much insulin will be needed to correct the premeal glucose? 2 units
4. What total dose of insulin should be taken? 9 units

CASE 2 Answers

Hayley has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 28 units daily
Bolus Insulin: C:I ratio = 12:1, CF = 45:1, BG Target = 100 mg/dL
Premeal BG = 235 mg/dL
Planned Meal:
Small corn tortilla (10 g)
Cooked rice – ⅓ cup (15 g)
Fruit juice – 1 cup (30 g)
Banana – 6-inch (30 g)

1. How many grams of carbohydrate does this meal contain? 85 g
2. How much insulin will be needed to cover the carbohydrates? 7.1 units
3. How much insulin will be needed to correct the premeal glucose? 3 units
4. What total dose of insulin should be taken? 10.1 units

CASE 3 Answers

Chloe has type 1 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 18 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 50:1, BG Target = 120 mg/dL
Premeal BG = 220 mg/dL
Planned Meal:
Cooked pasta – 1 cup (45 g)
Peas – ½ cup (15 g)
Small roll (15 g)
Wine cooler (30 g)

1. How many grams of carbohydrate does this meal contain? 105 g
2. How much insulin will be needed to cover the carbohydrates? 7 units
3. How much insulin will be needed to correct the premeal glucose? 2 units
4. What total dose of insulin should be taken? 9 units

CASE 4 Answers

Mac has type 2 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 36 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 25:1, BG Target = 100 mg/dL

Premeal BG = 175 mg/dL
Planned Meal:
Eggs, scrambled – 2 (0 g)
Toast – 2 slices (30 g)
Honey – 1 teaspoon on each piece of toast (10 g)
Fruit juice – 1 cup (30 g)

1. How many grams of carbohydrate does this meal contain? 70 g
2. How much insulin will be needed to cover the carbohydrates? 9 units
3. How much insulin will be needed to correct the premeal glucose? 3 units
4. What total dose of insulin should be taken? 12 units

CASE 5 Answers

Gene has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 32 units daily
Bolus Insulin: C:I ratio = 10:1, CF = 35:1, BG Target = 110 mg/dL
Premeal BG = 180 mg/dL
Planned Meal:
Beef – 6 oz (0 g)
Baked potato – medium (30 g)
Corn – ½ cup (15 g)
Microbrew beer – one (30 g)
Regular beer – one (15 g)

1. How many grams of carbohydrate does this meal contain? 90 g
2. How much insulin will be needed to cover the carbohydrates? 9 units
3. How much insulin will be needed to correct the premeal glucose? 2 units
4. What total dose of insulin should be taken? 11 units

CASE 6 Answers

Katy has type 1 diabetes mellitus and manages this with an insulin pump as follows.

Basal Insulin: 22 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 50:1, BG Target = 120 mg/dL
Premeal BG = 195 mg/dL
Planned Meal:
Grilled cheese sandwich (30 g)
Mashed potatoes – 1 cup (30 g)
Banana – 6-inch (30 g)
Regular soda – 12 oz (40 g)

1. How many grams of carbohydrate does this meal contain? 130 g
2. How much insulin will be needed to cover the carbohydrates? 8.7 units
3. How much insulin will be needed to correct the premeal glucose? 1.5 units
4. What total dose of insulin should be taken? 10.2 units

CASE 7 Answers

Emily has type 2 diabetes mellitus and manages this with multiple daily injections as follows.

Basal Insulin: 38 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 25:1, BG Target = 110 mg/dL
Premeal BG = 210 mg/dL
Planned Meal:
Eggs, fried – 2 (0 g)
Bacon – 2 slices (0 g)
French toast – 2 slices (30 g)
Banana, sliced – 3-inch (15 g)
Powdered sugar – 1 teaspoon (4 g)
Tea with honey - 1 teaspoon - (5 g)

1. How many grams of carbohydrate does this meal contain? 54 g

2. How much insulin will be needed to cover the carbohydrates? 7 units
3. How much insulin will be needed to correct the premeal glucose? 4 units
4. What total dose of insulin should be taken? 11 units

CASE 8 Answers

Leonard has type 1 diabetes mellitus and manages this with an insulin pump as follows.
Basal Insulin: 26 units daily
Bolus Insulin: C:I ratio = 12:1, CF = 40:1, BG Target = 100 mg/dL
Premeal BG = 200 mg/dL
Planned Meal:
Baked chicken – 2 pieces (0 g)
Mashed potatoes – 1 cup (30 g)
Peas – 1 cup (30 g)
Milk – 1 cup (12 g)

1. How many grams of carbohydrate does this meal contain? 72 g
2. How much insulin will be needed to cover the carbohydrates? 6 units
3. How much insulin will be needed to correct the premeal glucose? 2.5 units
4. What total dose of insulin should be taken? 8.5 units

CASE 9 Answers

Sonja has type 1 diabetes mellitus and manages this with an insulin pump as follows.
Basal Insulin: 24 units daily
Bolus Insulin: C:I ratio = 15:1, CF = 60:1, BG Target = 110 mg/dL
Premeal BG = 200 mg/dL
Planned Meal (Friday Night):
Beef – 8 oz (0 g)
Corn tortillas, small – 3 (30 g)
Rice – 2/3 cup (30 g)
Margarita – 8 oz (60 g)

1. How many grams of carbohydrate does this meal contain? 120 g
2. How much insulin will be needed to cover the carbohydrates? 8 units
3. How much insulin will be needed to correct the premeal glucose? 1.5 units
4. What total dose of insulin should be taken? 9.5 units

CASE 10 Answers

Henry has type 2 diabetes mellitus and manages this with multiple daily injections as follows.
Basal Insulin: 42 units daily
Bolus Insulin: C:I ratio = 8:1, CF = 30:1, BG Target = 120 mg/dL
Presnack BG = 210 mg/dL (4 hours after lunch)
Planned Snack:
Oreo cookies – 4 (30 g)
Milk – 1 cup (12 g)

1. How many grams of carbohydrate does this meal contain? 42 g
2. How much insulin will be needed to cover the carbohydrates? 5 units
3. How much insulin will be needed to correct the premeal glucose? 3 units
4. What total dose of insulin should be taken? 8 units

9. How do you assess if your patients are counting their carbohydrates accurately?

There are numerous carbohydrate counting quizzes and other assessment tools available on the internet. Here is one we use with our patients and our providers to assess and improve their carbohydrate counting skills. This is adapted from one used at the Cleveland Clinic. Try it.

University of Colorado Hospital: Carbohydrate Counting Quiz

Name: ______________________________ Date: ________________

Food	***Does this food contain carbohydrates? (Circle only one answer)***		
1. Bread	Yes	No	Don't Know
2. Breakfast sausages	Yes	No	Don't Know
3. Baked potato	Yes	No	Don't Know
4. Maple syrup, regular	Yes	No	Don't Know
5. American cheese	Yes	No	Don't Know
6. Low-fat milk	Yes	No	Don't Know
7. Apple juice	Yes	No	Don't Know
8. Soda pop (not diet)	Yes	No	Don't Know
9. Apple	Yes	No	Don't Know
10. Cooked dried beans (lentils, navy beans)	Yes	No	Don't Know

Food	***How many grams of carbohydrate does this portion contain? (Circle only one answer)***						
11. 1 cup milk	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
12. 1 cup pasta	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
13. 1 cup cooked Rice	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
14. 1 cup juice	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
15. 1 cup hot cereal	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
16. 1 cup cooked dried beans	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know
17. 1 cup mashed potatoes	0 g	15 g	30 g	45 g	60 g	75 g	Don't Know

For each question circle the best answer below.

18. Read the Nutrition Facts label to the right, what is the serving size?
    Don't know   1 cup   2 cups   4 cups
19. How many grams of carbohydrate would you consume if you ate one serving?
    Don't know   228 g   5 g   31 g
20. How many grams of carbohydrate would you consume if you ate the whole package?
    Don't know   456 g   10 g   62 g

Nutrition Facts

Serving Size 1 cup (228 g)
Servings Per Container 2

Amount Per Serving

Calories 260 Calories from Fat 120

	% Daily Value*
Total Fat 13 g	**20%**
Saturated Fat 5 g	**25%**
Cholesterol 30 mg	**10%**
Sodium 660 mg	**28%**
Total Carbohydrate 31 g	**10%**
Dietary Fiber 0 g	**0%**
Sugar 5 g	
Protein 5 g	

Vitamin A 4% • Vitamin C 2%
Calcium 15% • Iron 4%

*Percent daily values are based on a 2000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2000	2500
Total Fat	Less than	65 g	80 g
Sat Fat	Less than	20 g	25 g
Cholesterol	Less than	300 mg	300 mg
Sodium	Less than	2400 mg	2400 mg
Total Carbohydrate		300 g	375 g
Dietary Fiber		25 g	30 g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Number of correct answers: ____________
Percent correct answers: ___________ % (# Correct/20 × 100)
Answers to the quiz:
1. Yes 2. No 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes
11. 15 g 12. 30 g 13. 45 g 14. 30 g 15. 30 g 16. 30 g 17. 30 g 18. 1 cup 19. 31 g 20. 62 g

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KEY POINTS

- Precise mealtime insulin dosing requires accurate carbohydrate counting and an appropriate carbohydrate-to-insulin ratio (C:I ratio) that produces a premeal to 2-hour postmeal blood glucose (BG) excursion of 30–50 mg/dL.
- The C:I ratio is an estimate of the grams of carbohydrate that each 1 unit of insulin will cover; a C:I ratio of X:1 means that 1 unit of insulin should be given for each X grams of carbohydrate to be consumed. The initial C:I ratio for each person is often calculated as follows: 500/TDD of insulin.
- A CF is the amount of insulin that should be added to the mealtime dose when the premeal BG is above the target range or that is taken between meals to correct high BG values. The CF is an estimate of the expected BG drop for each 1 unit of insulin given when the BG is elevated above the goal; a CF of N:1 means that a person should take 1 unit of insulin for every N mg/dL the current BG level is above the individualized target. We calculate an initial CF for each person as 1650/TDD.

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APPS

Calorie Count: www.caloriecount.com/apps
Calorie King: www.calorieking.com/foods
Dbees: www.dbees.com
Diabetes App: https://itunes.apple.com/us/app/diabetes-app-blood-sugar-control/id387128141?mt=8
Diabetes Pilot: http://www.diabetespilot.com/
Diabetic Connect: http://www.diabeticconnect.com/
Figwee: https://itunes.apple.com/us/app/figwee-portion-explorer/id435839234?mt=8
Fit Day: www.fitday.com
Fooducate: https://play.google.com/store/apps/details?id=com.fooducate.nutritionapp&hl=en
Glooko: https://www.glooko.com/
Glucool Diabetes: https://play.google.com/store/apps/details?id=com.michaelfester.glucool.lite
Glucose Buddy: www.glucosebuddy.com
GoMeals: www.gomeals.com
My Fitness Pal: www.myfitnesspal.com/
OnTrack Diabetes: https://play.google.com/store/apps/details?id=com.gexperts.ontrack
Spark People: www.sparkpeople.com
WaveSense Diabetes Manager: http://wavesense-diabetes-manager.appsios.net/

CHAPTER 7

Inpatient Management of Diabetes and Stress Hyperglycemia

Stacey A. Seggelke and R. Matthew Hawkins

1. How common is diabetes and/or stress hyperglycemia in the inpatient setting?

Diabetes is a growing epidemic with an estimated 1 out of every 10 people having a diagnosis of diabetes in the United States. One in five of these individuals do not know they have diabetes and may be diagnosed for the first time during a hospital admission. Rates of stress hyperglycemia vary by study, with an approximate 32% of critically ill and 30% of noncritically ill patients demonstrating elevated blood glucose levels.

2. What is considered hyperglycemia in the inpatient setting and why is it a concern?

The American Diabetes Association (ADA) defines hyperglycemia in hospitalized patients as a blood glucose (BG) level >140 mg/dL. Hyperglycemia in patients with or without diabetes is correlated with increased rates of infection due to inhibition of chemotaxis and phagocytosis and decreased production of superoxide radicals. Endothelial injury, mitochondrial dysfunction, and osmotic diuresis from elevated BG levels can lead to multiple organ failure. These complications can cause increased hospital length of stay, morbidity, and mortality. One study of general surgical patients found an estimated increased risk of infection by 30% for every 40 mg/dL rise in BG above 110 mg/dL.

3. What are the glycemic targets for the critically ill and noncritically ill patient populations?

The ADA recommends a glycemic goal of 140–180 mg/dL for most critically ill and noncritically ill patients. The glycemic goal can be further lowered to 110–140 mg/dL in select patients if it can be attained without hypoglycemia. Many patients with tight glycemic control in the outpatient setting prefer to have lower targets while hospitalized.

4. What are the Inpatient glycemic targets for pregnant patients?

BG goals for pregnancy are tighter than for the general population. Hyperglycemia during pregnancy is associated with many adverse outcomes including macrosomia, congenital abnormalities, fetal hyperinsulinemia, and fetal mortality. For patients with gestational diabetes, type 1 diabetes, and type 2 diabetes, the recommendations are a fasting blood glucose level <95 mg/dL, 1-hour postmeal blood glucose ≤140 mg/dL, and 2-hour postmeal blood glucose level ≤120 mg/dL. (See Chapter 8 for further discussion on treatment of diabetes and pregnancy.)

5. When should point-of-care (POC) BG testing be performed in the hospital setting?

Most patients who have diabetes should have point-of-care (POC) BG testing before meals, at bedtime, and with any change in clinical status. Before meals, testing should be done as close to the meal as possible but ideally within 30 minutes. For patients taking nothing by mouth or receiving medical nutritional therapy, POC BG testing is recommended every 4 to 6 hours. Patients experiencing hypoglycemia, hyperglycemia, or other special circumstances may need POC BG testing more frequently. If the clinical situation does not match the POC BG result, such as asymptomatic hypoglycemia, laboratory testing should be done to confirm the result.

6. Should a hemoglobin A1C level be checked in inpatients?

In all patients with diabetes or hyperglycemia, hemoglobin A_{1c} (A_{1c}) should be checked on admission unless they have had a value within the past 3 months. The A_{1C} result can help evaluate home glycemic control and aid in discharge planning. In patients without a prior diabetes diagnosis, an A_{1C} >6.5% is very suspicious for undiagnosed diabetes prior to the hospital stay. If the A_{1C} is <6.4%, this does not exclude a diagnosis of diabetes, and further testing should be done in the outpatient setting. Common inpatient comorbidities such as anemias, end-stage renal disease,

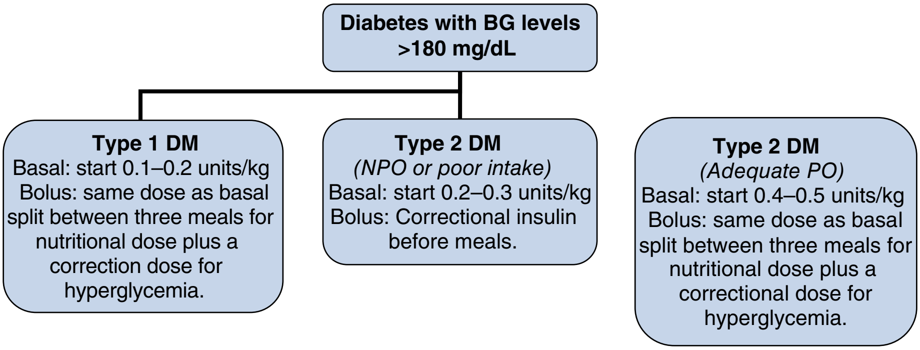
Diabetes with BG levels >180 mg/dL
Type 1 DM
Basal: start 0.1–0.2 units/kg
Bolus: same dose as basal split between three meals for nutritional dose plus a correction dose for hyperglycemia.
Type 2 DM
(NPO or poor intake)
Basal: start 0.2–0.3 units/kg
Bolus: Correctional insulin before meals.
Type 2 DM
(Adequate PO)
Basal: start 0.4–0.5 units/kg
Bolus: same dose as basal split between three meals for nutritional dose plus a correctional dose for hyperglycemia.

Fig. 7.1 Treatment of inpatient hyperglycemia.

end-stage liver disease, pregnancy, and sickle cell disease/trait and treatments such as recent blood transfusions or erythropoietin therapy can alter A_{1C} results.

7. What can cause hyperglycemia in hospitalized patients?

Increased production of counter-regulatory hormones (cortisol, epinephrine, glucagon, and growth hormone) and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) can lead to hyperglycemia through increased hepatic glycogenolysis and gluconeogenesis, lipolysis, and muscle catabolism. In addition, therapeutic interventions including glucocorticoid therapy, enteral or parenteral nutrition, and/or immunosuppressive agents increase the risk of hyperglycemia, especially in patients with preexisting diabetes. If hyperglycemia occurs, appropriate treatment should be initiated with glycemic goals of 140–180 mg/dL.

8. What is the best way to manage diabetes in hospitalized patients?

Insulin therapy, given as an intravenous infusion or subcutaneous injections, is the safest and most effective way to treat hyperglycemia in the hospital setting. The ADA recommends initiation of insulin therapy for treatment of hyperglycemia at a glucose threshold ≥180 mg/dL. Insulin therapy should then be titrated to maintain glycemic levels between 140–180 mg/dL. Insulin is effective and can be rapidly adjusted to adapt to changes in glucose levels or food intake. Standardized insulin protocols are recommended to be used whenever available (see Fig. 7.1).

9. Does evidence support intensive management of blood glucose in the inpatient setting?

It is well established that hyperglycemia and severe hypoglycemia contribute to adverse outcomes. There is controversy over what degree of glycemic control is most appropriate. The landmark inpatient surgical study, the Leuven Surgical ICU study, demonstrated a reduction in mortality by 34% in patients with a BG goal of 80–110 mg/dL compared to those with a goal of 180–200 mg/dL. This initial study called for tight glycemic control, especially in the critical care setting. However, subsequent studies could not replicate these results and found that tight glycemic control increased risk of hypoglycemia and mortality. The Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study was a large, multicenter, randomized controlled trial (RCT) that showed an increased risk of mortality in patients with tight glycemic control (BG target 81–108 mg/dL) as compared to those with standard glycemic control (BG target 144–180 mg/dL). The increase in mortality was thought to be partially due to the high rate of hypoglycemia (≤40 mg/dL) in the intensively treated group. While this study corroborated previous suggestions that glycemic control is important, it did underscore the risks of hypoglycemia and recommended relaxing of glycemic targets. Thus, inpatient glycemic BG targets were modified to 140–180 mg/dL to reduce the risk of hypoglycemia.

10. What is an intravenous insulin infusion and why is it used in critically ill patients?

An intravenous insulin infusion or insulin drip (gtt) is composed of 1 unit of regular human insulin per 1 ml of 0.9% NaCl (normal saline). When given intravenously, regular insulin has a rapid onset and short half-life (5–7 minutes), allowing for quick adjustment of insulin doses to achieve appropriate glycemic control.

11. How should the IV insulin infusion rate be started and adjusted?

An insulin infusion is usually initiated at 0.1 unit/kg (body weight)/hr. Insulin infusions should be adjusted on an hourly basis. Dosage adjustments should be made based on the current BG level and rate of change from the previous BG level. If the BG levels do not change by 30–50 mg/dL in an hour, the insulin infusion rate should be increased. Conversely, if BG levels drop more than 30–50 mg/dL in an hour, the insulin drip rate should be reduced. It is recommended that written insulin infusion protocols or computer-generated algorithms be used; they should include the following key elements.

12. How do I transition a patient off an insulin infusion?

Due to the short duration of action of IV regular insulin (5–7 minutes), it is ideal to give basal insulin (long-acting or intermediate-acting) SC 2–4 hours before or rapid-acting insulin SC 1–2 hours before discontinuation of the insulin infusion. Appropriate transition from IV insulin to scheduled SC insulin is important to decrease the risk of rebound hyperglycemia. This is especially imperative in patients with type 1 diabetes in whom just a few hours without insulin can result in diabetic ketoacidosis. Three different methods to transition from an insulin infusion to subcutaneous insulin are presented below.

1. Resume home basal doses and order bolus insulin according to PO intake (see below). This works well for people with good glycemic control prior to hospitalization (A1c ≤8%)
2. Calculate a weight-based basal insulin and order Lispro according to PO intake (see below).
3. Calculate basal and bolus doses based on the total daily dose (TDD) of insulin given via insulin infusion. First, determine the average rate (units/hour) of insulin infusion over the previous 6 hours. Next, multiply this average hourly rate x 24 hours to calculate the TDD of insulin the patient has received while on the insulin gtt. Then, multiply the TDD by 0.8 to decrease the risk of hypoglycemia after the transition to subcutaneous insulin. If the patient has *not* been eating on the insulin gtt, this new TDD is the estimated amount of basal insulin they will require. If the patient *has* been eating while on the insulin gtt, the TDD represents the combination of basal and bolus subcutaneous insulin the patient will need. This TDD should be divided into basal and bolus insulin components. Give 50–60% of the TDD as long-acting basal insulin and 40–50% of the TDD as rapid-acting insulin in three divided doses with meals.

13. How should you select a basal insulin dose if the patient is not on an insulin infusion?

Basal coverage can be achieved using intermediate-acting insulin (NPH) dosed twice daily or, preferably, long-acting insulin (glargine) dosed once or twice a day. Long-acting insulins are preferred, as they provide more consistent coverage with minimal insulin peaks. NPH insulin is more likely to cause hypoglycemia due to variable insulin action and peaks. Degludec insulin has been shown to reduce hypoglycemia in the outpatient setting. However, its long duration of action makes inpatient titration difficult; therefore, it is not recommended for inpatient use. Regardless of the type of insulin used, the basal insulin dose usually accounts for approximately 50% of the TDD of insulin.

Before continuing a home basal insulin dose, one should assess the current A1c, reported home BG levels, and occurrence of hypoglycemia. It is common for a patient's outpatient basal doses to cover their basal needs plus some postprandial glucose rises. If a patient reports hypoglycemia at home, especially nocturnal, a decrease in the basal dose of 20–50% may be warranted.

The initial basal dose can be based on diabetes type and the patient's nutritional status. For patients with Type 1 diabetes or those who have had a total pancreatectomy (TP), a starting basal dose of 0.1–0.2 units/kg is appropriate. In patients with type 1 diabetes or TP, *basal insulin is always needed*, including when they are NPO. For patients with type 2 diabetes who are NPO or have poor PO intake, a starting basal dose of 0.2–0.3 units/kg is usually appropriate. A recommended starting basal dose for patients with Type 2 diabetes with insulin resistance and adequate oral intake is 0.4–0.5 units/kg.

TABLE 7.1 Target Glucose Levels for Hospitalized Patients

Critically Ill: 140–180 mg/dL
Noncritically Ill: 140–180 mg/dL
Pregnant: fasting <95 mg/dL, 1 hr postprandial ≤140 mg/dL; 2 hrs postprandial ≤120 mg/dL

Adapted from: American Diabetes Association Professional Practice Committee; 16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S321–S334. https://doi.org/10.2337/dc25-S016

TABLE 7.2 Treatment of Hyperglycemia Inpatient

Insulin is the most appropriate treatment agent for hyperglycemia in the hospital
Intravenous Insulin Infusion is the best therapy for critically ill patients
Basal/Bolus (prandial and correction) insulin is the best therapy for noncritically ill patients
Blood glucose levels should be evaluated daily, and insulin adjusted as needed

Adapted from: American Diabetes Association Professional Practice Committee; 16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S321–S334. https://doi.org/10.2337/dc25-S016

TABLE 7.3 Key Elements of an Intravenous Insulin Infusion Protocol

• Identify appropriate BG targets
• Nurse-driven, easy-to-use insulin titration protocols
• Frequent POC BG checks and insulin adjustments
• Titration based on direction of change in glucose (decrease, no change, increase)
• Titration based on velocity of change (decrease rate faster if larger drop in BG values)
• Included guidelines for treatment of hypoglycemia and subsequent adjustment of insulin rate

Adapted from: American Diabetes Association Professional Practice Committee; 16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S321–S334. https://doi.org/10.2337/dc25-S016

IMPORTANT

When renal impairment is present, insulin doses may need to be decreased due to risk of hypoglycemia from decreased insulin clearance/metabolism and decreased renal contribution to gluconeogenesis.

14. How should you select a prandial dose for patients on insulin?

Prandial insulin should include both nutritional (meal coverage) and correctional (treatment of hyperglycemia) components. Rapid-acting insulin analogs (Lispro, Aspart, Glulisine) should ideally be given 0 to 15 minutes prior to meals whereas short-acting insulin (regular) should be given 30 minutes prior to meals. Rapid-acting analogs provide increased flexibility in dosing and have a shorter duration of action, making them the preferred method of treatment. In general, the total bolus insulin doses each day should be about 40–50% of the TDD of insulin delivery. However, in the hospital setting, a reduced prandial dose may be needed due to decreased appetite or variance in PO intake. Correctional insulin dosing can be calculated based on the patient's insulin sensitivity. This insulin is either added to the nutritional dose or given alone if the patient is not receiving calories. For patients with Type 1 diabetes or who are insulin sensitive, a good starting point for correction dosing is 1 unit of insulin for every 50 mg/dl above a goal of 100 mg/dl. For patients with Type 2 diabetes or insulin resistance, you can use 1 unit of insulin for every 25 mg/dL above 100–150 mg/dl (see Table 7.4 for examples). Additionally, if the person's home insulin doses are known, the correction dose can be estimated by dividing 1600 by their TDD of insulin; this equation is different in other circumstances and other regions of the United States (varies from dividing 1500 up to 1800 by the TDD, depending on the probable insulin

TABLE 7.4 Example of Nutritional and Correctional Insulin Dosing Chart

BLOOD GLUCOSE mg/dL	☐ **SENSITIVE TO INSULIN**		☐ **RESISTANT TO INSULIN**		☐ **EXTRA RESISTANT TO INSULIN**		☐ **CUSTOMIZED**	
	Type 1 DM Stress Hyperglycemia Normal body weight		Type 2 DM Steroids Overweight/Obese		Blood Glucose uncontrolled by “Resistant to Insulin” Table			
≤70	Implement Hypoglycemia orders		Implement Hypoglycemia orders		Implement Hypoglycemia orders		Implement Hypoglycemia orders	
	Receiving Calories	No Calories	Receiving Calories	No Calories	Receiving Calories	No Calories	Receiving Calories	No Calories
71–124	3 units	No Insulin	6 units	No Insulin	10 units	No Insulin	_____units	_____units
125–149	3 units	No Insulin	7 units	1 unit	12 units	1 unit	_____units	_____units
150–199	4 units	1 unit	8 units	2 units	14 units	3 units	_____units	_____units
200–249	5 units	2 units	10 units	4 units	16 units	5 units	_____units	_____units
250–299	6 units	3 units	12 units	6 units	18 units	7 units	_____units	_____units
300–349	7 units	4 units	14 units	8 units	20 units	9 units	_____units	_____units
350–399	8 units	5 units	16 units	10 units	22 units	11 units	_____units	_____units
≥ 400	Call MD		Call MD		Call MD		Call MD	

TABLE 7.5 Contraindications to Insulin Pump Use in the Hospital

CONTRAINDICATIONS TO INSULIN PUMP USE IN THE HOSPITAL
Altered mental status
Suicidal ideation
Diabetic ketoacidosis
Concern for insulin pump malfunction
Lack of appropriate supplies for the insulin pump
Patient/family inability to participate in pump self-management

sensitivity of the local population). To prevent hypoglycemia due to "stacking" of insulin, correctional insulin doses should not be given more often than every 4 hours.

15. How should you adjust insulin dosages?

BG should be assessed multiple times daily by POC testing or continuous glucose monitoring (CGM). Basal insulin doses are analyzed by reviewing fasting BG levels compared to HS BG levels. With ideal basal insulin doses, BG levels should remain stable through the night; a significant BG rise or drop overnight necessitates a change in basal insulin dosing. Prandial insulin is assessed by prelunch, predinner, and bedtime BG values. If BG levels rise during the day after oral intake, bolus insulin doses should be increased. Similarly, if oral intake is stable and BG levels decrease during the day, a decrease in bolus insulin is recommended. For more precise prandial dosing, a 2-hour postprandial BG check can be performed. It is expected that the postprandial value will be about 30–50 mg/dL above the preprandial reading.

16. Is sliding-scale insulin still used?

Traditional sliding-scale insulin is not effective for hyperglycemia and should not be used. A sliding scale is a set amount of bolus insulin, usually regular insulin, which was given to treat high BG levels, above 200 mg/dl. Insulin was given without thought as to mealtimes, previous dosages, carbohydrate content of meals, or the patient's insulin sensitivity. This often resulted in a wide fluctuation of BG levels because hyperglycemia was not treated preemptively but instead was treated after the fact.

17. What is hypoglycemia and what contributes to it?

Hypoglycemia is defined as a BG level <70 mg/dL, which is considered the initial threshold for counter-regulatory hormone release. The ADA further classifies hypoglycemia as follows:

Level 1: BG <70 mg/dL and ≥ 54 mg/dL.
Level 2: BG <54 mg/dL.
Level 3: severe hypoglycemic event (any glucose level) where the person has altered mental or physical status and requires assistance for treatment of hypoglycemia.

Patients at elevated risk for hypoglycemia include those with renal or liver disease/failure, altered nutrition, older age, sepsis, and history of severe hypoglycemia.

18. How should hypoglycemia be treated?

Hypoglycemia treatment depends on the situation. For people who can have oral intake, 15–30 g of quick acting carbohydrates such as juice, regular soda, or glucose tablets/gel is the preferred treatment. If the person is unconscious or cannot take carbohydrates orally, 50 g (1 ampule) of Dextrose 50% can be given IV or 1 mg of glucagon can be given IM. This is also the preferred treatment for people with Level 2 hypoglycemia in the hospital setting. Glucose levels should be rechecked 15–20 minutes after treatment to assess efficacy. If the BG level is still <70 mg/dL, treatment should be repeated.

19. Are oral agents or noninsulin injectable medications appropriate to use in hospitalized patients?

There is limited data on the safety and efficacy of using oral agents or noninsulin injectable medications in hospital settings. In most cases of hyperglycemia, noninsulin treatment options are not effective in lowering BG to target levels, especially in acute illness. Recent studies have demonstrated the safety of using Dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin and sitagliptin) in the hospital setting. When used alone or in combination with basal insulin or correctional bolus insulin, DPP-4 inhibitors proved to be an effective treatment. Caution is recommended with the use of saxagliptin and alogliptin in patients with heart or kidney disease because of a potential increased risk of heart failure, according to an FDA safety communication. Safety concerns for other oral agents include risk of lactic acidosis with metformin and delayed onset of action and fluid retention with thiazolidinediones. Sodium–glucose cotransporter 2 (SGLT2) inhibitors are unique to the inpatient setting, as they are used not only to treat diabetes but also as first-line therapy for patients with heart failure with or without diabetes. The ADA recommends continuing these medications in patients with heart failure during their hospital stay if they are not acutely ill and have no other contraindications. Risks of continuing these medications are dehydration, hypotension, urinary or genital tract infections, and euglycemic DKA with NPO status. A recent study by the Veterans Health Administration showed a decreased mortality rate and length of stay if SGLT2 inhibitors were continued during an inpatient stay. Oral agents may be initiated or resumed in clinically stable patients close to discharge. Inpatient use of noninsulin injectable medications, such as GLP-1 receptor agonists or dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) therapies, for management of hyperglycemia is not recommend due to known gastrointestinal side effects, including the risk of ileus.

20. What is the best treatment for steroid-induced hyperglycemia?

Steroids cause insulin resistance and diminished insulin secretion, manifested by excessive postprandial BG excursions. The degree of BG elevation depends on the type, amount, and duration of steroid use. Individuals who are insulin naïve and on low doses of steroids may be treated with bolus insulin at mealtimes. If the person is receiving higher doses of steroids (Prednisone 20 mg daily or equivalent dose) or has a history of insulin-treated diabetes, an effective treatment option is intermediate basal insulin. NPH insulin can be given at the same time as administration of the steroid. The NPH dose is based on the patients' weight and steroid dose. One recommended regimen is 0.1 unit/kg NPH insulin for each 10 mg of prednisone equivalent to a maximum of 0.4 units/kg for doses ≥ 40 mg of prednisone equivalent. For patents on steroids with a long duration of action, such as dexamethasone, or multiple daily doses of shorter-acting steroids, long-acting basal insulin may be used. Insulin needs should be assessed and adjusted with tapering or discontinuation of steroid therapy. If BG levels remain uncontrolled with subcutaneous therapy, IV insulin may be needed.

21. What is the best treatment for hyperglycemia with parenteral nutrition?

For parenteral nutrition (PN), the addition of regular insulin to the PN bag is the safest approach to glycemic control. The initial dosing recommendation is 1 unit of regular insulin for every 10–12 grams of dextrose in the PN solution for patients with type 2 diabetes or 1 unit for every 15–20 grams of dextrose for patients with type 1 diabetes or those who are insulin naive. A rapid-acting insulin correction scale every 4–6 hours is also recommended to correct hyperglycemia if the initial dose of regular insulin in the PN is not adequate. The TDD of correctional insulin needed to maintain euglycemia can be added to the total regular insulin dose in the PN the next day.

22. What is the best treatment for hyperglycemia with enteral nutrition?

There are many approaches to treatment for people receiving enteral nutrition (EN). Depending on whether EN is continuous or cyclic, long-acting insulin (for continuous EN) or intermediate-acting insulin (for cyclic EN) can be administered once or twice daily in combination with a rapid-acting insulin correction scale every 4–6 hours. Alternatively, intermediate-acting 70/30 human insulin given every 8 hours with a correctional rapid acting scale every 4 hours is an approach that the authors use. For patients who are on volume-based EN, where the EN infusion can vary to reach a daily total volume, the use of variable lispro dosing every 4 hours based on the infusion rate can be used. Hypoglycemia is a concern in these patients, since feeding can be interrupted unexpectedly with dislodging of the feeding tube or discontinuation of the EN due to nausea or diagnostic testing. It is important that all EN insulin orders recommend that a dextrose containing IV solution, such as D10W, be initiated at the same rate as the EN, if nutritional therapy is unexpectedly interrupted. Reducing or holding the next dose of long- or intermediate-acting insulin may also be necessary. Additionally, these patients are in a consistent postprandial state, so glucose goals should be adjusted accordingly with a general goal of BG levels <180 mg/dL.

23. Can concentrated insulins be used in the hospital?

Concentrated insulin use in the outpatient setting has become more common, but there are many concerns with continuing this regimen in the inpatient setting. U-500 regular insulin is a concentrated insulin that delivers five times the number of units in the same volume as U-100 insulin. It may be used as a subcutaneous injection or in continuous subcutaneous insulin infusions. Because of its concentration, there is potential for adverse events related to insulin dosing. To decrease the risk, U-500 specific syringes are recommended; pharmacy staff should confirm the dosing and deliver predrawn syringes for each person. However, most people who use U-500 at home do not need to continue using it in the hospital. One study found that people required significantly lower doses of insulin while hospitalized and that glucose could be managed with conventional insulin formulations.

Other concentrated insulin preparations on the market, such as insulin glargine 300 U/mL, insulin degludec 200 U/mL, and insulin lispro 200 U/mL, come in pen devices that adjust the volume of insulin given to avoid calculation errors. The efficacy and safety of these insulins in the hospital setting have not been determined.

24. Can a continuous subcutaneous insulin infusion be used in the inpatient setting?

Continuous subcutaneous insulin infusion (CSII), also known as an insulin pump, can often be safely used in the inpatient setting. Many people who are well controlled on an insulin pump as outpatients will become frustrated if the insulin pump is removed during their inpatient stay. To safely continue CSII inpatient, the person must be mentally and physically able to operate their own insulin pump. It is also recommended that personnel with CSII experience help manage the patient while admitted. For patient and staff safety, an insulin pump agreement should be completed that outlines expectations that the person will collaborate with the hospital team and report any BG levels not performed by hospital staff, all boluses given for nutritional or correctional coverage, and any symptoms of hypoglycemia. Current pump settings including basal rates, bolus settings, and bolus dosages should be documented daily by the treating hospital team. In addition, the treatment team should review the TDD of insulin delivered the prior day. For patients with either a hybrid closed-loop pump or a bionic pancreas pump, the glucose goals should be liberalized to meet inpatient glycemic goals and reduce the risk of hypoglycemia. It should also be noted that the algorithms for auto-adjustment of insulin pumps may not react quickly enough to adjust for special situations in the inpatient setting (steroids, PN, EN), and people may need additional subcutaneous insulin through injections and/or have the pump discontinued. Insulin pump companies recommend disconnection or removal of pumps for many tests where there is a risk of exposure to x-rays, radiation, or MRIs. People that use a continuous glucose monitor (CGM) with their insulin pump should be allowed to continue using this device in the hospital, but all insulin adjustments should be made based on finger-stick BG testing.

25. Can a continuous glucose monitor (CGM) be used in the inpatient setting?

Through testing of interstitial glucose levels, CGM provides current glucose values and a directional glucose trend. Alarms built into the CGM can alert patients to current or predicted hypo- or hyperglycemia. Most studies using either real-time or intermittently scanned CGM in the hospital setting showed reductions in hypoglycemia events but did not demonstrate overall improvement in glycemia. Use of a real-time or intermittently scanned CGM can be continued in the hospital; however, all insulin treatment decisions and hypoglycemia confirmation should be made based on finger-stick BG testing.

26. How do you adjust diabetes medications prior to surgery?

Hypoglycemia is a considerable risk for patients undergoing surgery because of their NPO status. Oral agents should be held the morning of the procedure. If a patient is on an SGLT2-inhibitor, this should be held for 72 hours prior to surgery due to the increased risk of euglycemic ketoacidosis when NPO. It is recommended that patients on long-acting insulin (glargine/detemir/degludec) take about 50–80% of their usual dose the night before or morning of surgery. Patients on intermediate-acting insulin (NPH) should take 50% of their typical dose the morning of the procedure. Correctional doses of rapid-acting insulin analogs can be given in the perioperative periods every 4 hours to maintain glycemic levels <180 mg/dL. If the procedure is prolonged or if prolonged NPO status is expected, the use of an insulin infusion is recommended.

27. How do I decide what home regimen to order at discharge?

If good glycemic control as an outpatient is documented, determined by an A1c drawn at admission, the patient can be sent home on the regimen she/he was on prior to admission. For patients with a new diagnosis of diabetes or those requiring a change in their previous therapy due to poor antecedent glycemic control, recommendations should be based on the patient's preference/ability, cost of, and contraindications to medications. Medication administration instructions, especially for insulin, should be given in both oral and written formats. Also details of discharge medications and instructions should be communicated promptly and clearly to the patient's outpatient diabetes provider. In addition, the patient's diabetes self-management knowledge should be assessed prior to discharge, including understanding of their diabetes diagnosis, self-monitoring of BG, glycemic goals, hypoglycemia treatment, sick day management, and how/when to take glucose lowering medications.

28. What is unique about treating diabetes patients with COVID-19?

COVID-19 has provided a unique challenge in inpatient diabetes management. It is well established that patients with uncontrolled diabetes who contract COVID-19 have more severe disease progression and an increased mortality risk. Many of these patients have severe insulin resistance requiring 300–500 units of insulin/day to maintain euglycemia while in the ICU. These extreme insulin requirements are likely secondary to the acute inflammatory and metabolic effects of COVID-19 and the need for medical nutrition and steroid therapy. A significant reduction in insulin requirements occurs with clinical improvement. Vigilant monitoring of glucose levels is imperative.

WEBSITES

American Association of Clinical Endocrinologist Inpatient Glycemic Control Resource Center.http://resources.aace.com

American Diabetes Association Standards of Diabetes Care 2024—Diabetes Care in the Hospital.https://care.diabetesjournals.org/content/43/Supplement_1/S193

Center for Disease Control and Prevention Diabetes Home Page.https://www.cdc.gov/diabetes/index.html

Society of Hospital Medicine Glycemic Control Resource Room. http://www.hospitalmedicine.org/ResourceRoomRedesign/RR_LandingPage.cfm

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CHAPTER 8

Diabetes in Pregnancy

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1. How does normal pregnancy affect fuel metabolism?

Pregnancy is a complex and orchestrated metabolic state that is necessary to provide adequate nutrients for the growing fetal–placental unit. Metabolic changes across pregnancy involve marked alterations in steroid and protein hormone production that include increases in estrogen, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone (GH), and human placental lactogen (hPL), increased inflammatory cytokines (tumor necrosis factor alpha [TNF-α], C-reactive protein, IL-6), and higher adipokines (leptin and adiponectin) to alter maternal fat accretion and insulin resistance. Cumulative data supports that the intrauterine metabolic environment characterized by over- or undernutrition may be a risk factor for abnormal fetal growth and future risk of childhood obesity.

2. What are the key preconception counseling recommendations among individuals with diabetes desiring pregnancy?

Health optimization in anyone desiring pregnancy is recommended prior to pregnancy to decrease the risk for perinatal complications. Women with preexisting diabetes that have evidence of microvascular and/or macrovascular disease or with suboptimal glycemic control (Hemoglobin A1C [HbA1C or A1C]) ≥6.5%) have significantly increased risks for adverse perinatal outcomes including but not limited to spontaneous abortion, congenital anomalies, diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome, fetal growth abnormalities, macrosomia, IUFD, preeclampsia, and cesarean deliveries. People with advanced stage nephropathy (creatinine ≥1.4 mg/dL) have higher risks for developing early-onset severe preeclampsia, fetal growth restriction, and functional renal decline requiring dialysis during the pregnancy. Due to increases in mitogenic growth factors, relative anemia, hypercoagulable state of pregnancy, and the rapid institution of tighter glycemic control, proliferative retinopathy can worsen with advancing gestation. Therefore preventing unplanned pregnancies should be a priority for all providers involved in the care of individuals of child-bearing age. Consistent with the American College of Obstetrics and Gynecology (ACOG), the American Diabetes Association (ADA) 2024 guidelines strongly support that, starting at puberty and continuing in all people with diabetes and childbearing potential, preconception counseling should be incorporated into routine diabetes care. Furthermore, family planning and effective contraception with consideration of long-acting, reversible contraception should be discussed and used until an individual's treatment plan and A1C are optimized.

Because nearly half of pregnancies in the United States are unplanned, a multidisciplinary team approach including a primary care provider, endocrinologist, obstetrician-gynecologist, maternal-fetal medicine, nutritionist, and psychologist are recommended to work together to provide preconception care and optimize health among individuals of childbearing age. Preconception care has been demonstrated to improve glycemia, perinatal mortality, preterm birth, and congenital malformations, reducing congenital anomalies by 71%. The goal to achieve a preconception A1C <6.5% through a multidimensional approach (i.e., healthy eating patterns, physical activity, exercise, adequate micronutrient supplementation, glycemic control, sleep hygiene, and mood stability) is fundamental to optimizing the intrauterine environment, as the majority of organogenesis is complete by 6 weeks postconception (8 weeks after the last menstrual period). To transition more smoothly to strict pregnancy targets, glycemic goals in the preconception period, using self-monitoring or CGM, are premeal glucose values of 80–110 mg/dl and 2-hr postprandial <155 mg/dL (average <126 mg/dL), while minimizing hypoglycemic events. Insulin is the recommended pharmacotherapy to achieve these targets if interventions to prevent pregnancy are not used. If metformin alone can achieve the glycemic targets, it can be continued prepregnancy and used safely in the first trimester.

Folic acid supplementation with 0.8–1 mg daily is recommended at least 3 months prior to conception to reduce the risk of defects of the neural tube, which is formed by 4 weeks postconception. Screening for abnormal thyroid function, retinopathy, nephropathy, neuropathy, cardiovascular disease, obstructive sleep apnea, and hypertension should be ordered and managed prior to conception if indicated. Medications should be reviewed and alternative medications that are safe in pregnancy should be prescribed. The risks of tobacco, alcohol, and cannabis use should be reviewed with shared goals for cessation implemented.

Women with diabetes are at high risk for depression, anxiety, sleep disorders, and eating disorders, all of which can affect glycemic control, perinatal and neonatal outcomes. Untreated obstructive sleep apnea (OSA) with undiagnosed pulmonary hypertension can result in maternal or infant hypoxemia and right heart failure. The risk of fetal exposure to untreated major depression is considered to be a greater concern than the risk of fetal exposure to the SSRI antidepressants. In addition, women with T1D are at risk for other autoimmune conditions such as celiac sprue and pernicious anemia (B12 deficiency) and also for vitamin D deficiency, iron deficiency, and hypothyroidism, which can independently impact pregnancy outcomes and should be screened for prepregnancy.

Referral to a dietitian to review nutritional status and pregnancy-specific challenges/expectations is advised. Women and families should be encouraged about healthy eating consisting of complex carbohydrates, soluble fiber, dairy, proteins, fruits, vegetables, and healthy fats while reducing levels of added sugars, sodium, and saturated fats. Providers should review the United States Preventive Services Task Force (USPSTF) and ACOG recommendations for physical activity (≥150 min cardiovascular exercise/week with ≤2 days of inactivity and ≥2 days/week of resistance activity) and goals should be encouraged to continue throughout the pregnancy.

3. How does pregnancy affect the morbidity and mortality of coronary artery disease among women with diabetes?

The United States has the highest incidence of myocardial infarction during pregnancy with rising rates over the past several decades, reflecting the increasing prevalence and contributions of advanced maternal age, obesity, hypertension, and diabetes complicating pregnancy. The cardiovascular system undergoes significant physiologic changes during pregnancy: decreased systemic vascular resistance but increased plasma volume, red blood cell mass, heart rate, stroke volume, cardiac output, ventricular wall muscle mass, and oxygen consumption. These changes are further challenged among women with preexisting cardiovascular disease, which may lead to inadequate oxygen supply to the myocardium. The morbidity and mortality rates of coronary artery disease are high in pregnant women with diabetes. Cardiac status should be assessed with functional testing (echocardiogram) before conception in those presenting with any microvascular disease, known coronary artery disease, and additional cardiac risk factors such as hyperlipidemia, hypertension, tobacco use, cardiac autonomic neuropathy, strong family history, or suggestive symptoms. A resting EKG should be considered for asymptomatic individuals aged 35 or older or those with diabetes for >10 years.

4. How should women on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers be counseled preconception and postpartum?

The goal of antihypertensive treatment is to maintain blood pressures at a level that minimizes maternal cardio- and cerebrovascular risk. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers taken for either renal protection or for hypertension in the second and third trimesters of pregnancy are associated with increased rates of fetal growth restriction, oligohydramnios, patent ductus arteriosus, neonatal hypotension refractory to treatment, and neonatal renal failure. A study of women with chronic hypertension, including more than 4100 pregnant women exposed to ACE inhibitors during the first trimester of pregnancy, found no significant increase in major congenital anomalies. Although older reviews supported that exposure to these agents in the first trimester increased cardiac and central nervous system malformations, many of the studies were confounded by other concurrent medication use and influence of comorbidities such as diabetes, cardiovascular disease, and obesity. Providers should discuss alternative agents to manage hypertension before pregnancy (calcium channel blocker, beta-blocker, labetalol, or hydralazine) with individuals who are considering pregnancy. Utilizing a multidisciplinary approach to optimize preconception health, women taking ACE inhibitors with significant renal disease may consider continuing them until pregnancy is confirmed for the reno-protective effects and then discontinuing them as soon as they have a missed period or positive pregnancy test.

During the postpartum period, women who are candidates for an ACE inhibitor (i.e., diabetes, hypertension, renal disease, hypertensive disorders of pregnancy, etc.) can be started on enalapril or captopril, which have not been shown to appear in breast milk in appreciable concentrations. A randomized controlled trial (RCT) investigating enalapril versus placebo in the postpartum period among participants who were diagnosed and delivered with preterm preeclampsia (<37 weeks) demonstrated better diastolic function and improved left ventricular remodeling at 6 months postpartum. Other antihypertensives with no known adverse effects on babies receiving breast milk include labetalol, nifedipine, verapamil, and hydralazine. Although there was no difference in antihypertensive medication use at discharge, an RCT by Perdigao et al. using furosemide for a short course postpartum demonstrated a reduction in persistent hypertension postpartum and faster recovery of blood pressures without impacting breastfeeding. Similarly, a study investigating furosemide versus placebo for the treatment of severe preeclampsia postpartum in conjunction with nifedipine demonstrated a significantly lower requirement of additional antihypertensive agents to achieve postpartum blood pressure goals with a short course of furosemide. However, chronic diuretic use without an indication as noted above is usually avoided due to possible concerns on the adequacy of breastfeeding.

5. How should women with diabetes be screened and treated for thyroid disease prior to pregnancy?

Because individuals with T1D have an increased risk of developing hypothyroidism from Hashimoto's thyroiditis and postpartum thyroiditis (three- to fourfold), thyroid screening with TSH is recommended preconception and first trimester. Some experts suggest thyroid screening be considered for individuals with T2D, secondary to the modest association with hypothyroidism and higher rates for developing diabetes. Women with known TPO antibody positivity should have TSH checked when pregnancy is confirmed and surveillance every 4–6 weeks until 18 weeks followed by every trimester because they are at risk for developing subclinical or overt hypothyroidism in pregnancy. About half of women with high TPO titers will develop postpartum thyroiditis. It is recommended that pregnant individuals with subclinical hypothyroidism with a TSH >4.0, especially if they have positive thyroid peroxidase (TPO) antibodies, are treated with levothyroxine (LT4) during the pregnancy; LT4 can be reevaluated postpartum for continuation of therapy.

6. Should statins or fibrates be discontinued before conception?

Statins and fibrates have not been correlated with increased teratogenicity despite the previous FDA X category (contraindicated for pregnancy) warning on statins. However, with the insufficient safety data for both drug classes during pregnancy, both are generally recommended to be discontinued during pregnancy. A multidisciplinary discussion for women with significant CAD, history of pregnancy-associated myocardial infarction, familial hyperlipidemia, or severe hypertriglyceridemia should be conducted to determine benefit/risk ratio for continuing these medications in pregnancy. Fibrates may be indicated for the treatment of hypertriglyceridemia among women who are refractory to high-dose fish oil (4 g of omega-3 fatty acids), as well as nutritional and lifestyle modifications to prevent pancreatitis, with gemfibrozil being preferred over fenofibrate due to more data on the former. Often exposure to fibrates in the first trimester can be avoided, but due to the two- to threefold rise in triglycerides during pregnancy, women are at an increased risk for pancreatitis with fasting triglyceride levels >400 mg/dL in early pregnancy, and treatment to lower triglycerides is indicated.

Lipophilic statins such as atorvastatin and lovastatin have had mixed reports regarding risks for fetal malformations, but hydrophilic statins such as pravastatin are minimally present in the embryo. Pravastatin has shown promise in animal models to improve abnormal vascular profiles and prevent growth restriction. In human primary endothelial cells, purified cytotrophoblast cells, and placental explants obtained from women with preterm preeclampsia, pravastatin reduced sFlt-1 secretion and improved markers of endothelial dysfunction. Costantine et al. performed a phase 1 clinical trial using low-dose 10-mg pravastatin among women at high risk for preeclampsia followed by a pilot RCT initiating 20-mg pravastatin versus placebo at 12 to 17 weeks' gestation, which demonstrated overall safety of pravastatin use in pregnancy. Clinical trials are still needed to determine the efficacy and neonatal safety of pravastatin for preeclampsia prevention, but there is no indication for their use to lower LDL cholesterol except in women at very high risk for cardiovascular events or severe hyperlipidemia such as familial hyperlipidemia.

7. Summarize the effect of smoking and cannabis during pregnancy.

Tobacco and cannabis use in pregnancy are associated with adverse perinatal and offspring outcomes. Both substances have evolved to include diverse products and availability at greater potencies. Smoking, smokeless tobacco, and second- and third hand smoke continue to be the leading environmental causes of low-birth-weight infants in women with and without diabetes. Tobacco use increases the risk for fetal growth restriction, placental abruption, abnormal placentation, altered thyroid function, preterm births, and perinatal mortality. Similarly, cannabis is also associated with higher rates of low birth weight, NICU admissions, placental abruption, and cognitive and behavior sequelae in the offspring. Both tobacco- and cannabis-related adverse outcomes increase in a dose-dependent manner. Children experience continued consequences of gestational tobacco exposure with higher rates of asthma, infantile colic, childhood obesity, and sudden infant death syndrome. Tobacco and cannabis use screening, cessation and risk reduction counseling, and goal setting are recommended before conception and every prenatal visit. The greatest reduction in tobacco risk is achieved with cessation earlier (<15 weeks) in pregnancy, but any cessation and reduction efforts even late in pregnancy to 18 months postpartum demonstrate positive benefits for perinatal and infant outcomes.

8. How does pregnancy affect diabetic nephropathy?

Diabetic nephropathy is a progressive disease and the leading cause of end-stage renal disease in the United States. The glomerular filtration rate increases nearly 50% during pregnancy, and proteinuria nearly always increases in pregnancy. Pregnancy is not associated with a greater decline in kidney function or impaired long-term maternal survival among women with normal serum creatinine prepregnancy as long as blood pressure and proteinuria are managed prior to conception and throughout gestation. Individuals with more severe renal insufficiency (chronic kidney disease stage 3–4 or estimated GFR <40 mL/min) typically have concomitant hypertension and proteinuria. They have high rates of SGA, preterm birth, cesarean births, preeclampsia, and progression of pregnancy-related loss of kidney function and/or end-stage renal disease during pregnancy or within the postpartum period, particularly in the setting of hypertension and significant proteinuria (>1 gm/24 hr).

9. Does nephropathy increase the risk of preeclampsia?

Preeclampsia complicates approximately 20% of pregnancies in women with preexisting diabetes and increases to nearly two-thirds in pregnancies complicated by nephropathy. The risk of preeclampsia is the highest among pregnant persons with hypertension, nephrotic range proteinuria, and abnormal renal function, particularly with a serum creatinine >1.4 mg/dl. Individuals with diabetic nephropathy and reproductive capacity should be counseled to have children when their glycemia is optimally controlled, blood pressure strictly managed, and preferably with mild nephropathy. Reproductive-age individuals with all degrees of renal disease or a renal transplantation can conceive. It is critical that they are counseled and use effective long-acting reversible contraception (LARC) for pregnancy to be planned and provided an opportunity for health to be optimized. A metabolically favorable progesterone-only contraceptive such as Drospirenone can also be considered.

Continuing renal protective antihypertensive medications such as ACE inhibitors and ATII blockers until the woman is ready for pregnancy can be considered among those with renal disease. However, to achieve stable blood pressures (<135/85 mmHg), combination therapy using antihypertensive agents with better safety profiles for pregnancy is often necessary. Low-dose aspirin in the first trimester is recommended as a preventative strategy for preeclampsia. Although studies have demonstrated potential benefit in the 60–150 mg/day range, the USPSTF recommends 81 mg/day as a reasonable dose for prophylaxis. A systematic review and meta-analysis demonstrated that aspirin doses of 150–162 mg were associated with a significant reduction of preterm preeclampsia compared with doses of 75–81 mg (472 participants; RR 0.34; 95% CI 0.15–0.79; $P = .01$; $I^2 = 0\%$) but not with a difference in preeclampsia at term.

Preeclampsia has been shown to increase the risk for long-term chronic kidney disease, kidney-related hospitalizations, and end-stage kidney disease, particularly among individuals who develop preterm preeclampsia. As less than 50% of individuals who become pregnant have good cardiometabolic health (nonsmoker, BMI <25 kg/m^2, absent diabetes or hypertension) prior to conception, providers should focus on the preconception or interpregnancy period for health optimization as the key period for reducing adverse perinatal and long-term disease in the offspring and the pregnant person.

10. How does renal transplantation affect pregnancy outcomes?

The overall acute rejection rates during pregnancy are similar to the general US nonpregnant population unless individuals stop their immunosuppressant agents for fear of pregnancy risks. Compared to pregnant persons with severe chronic kidney disease without a renal transplant, women who have had a successful renal transplant with near-normal renal function, intensive blood pressure control, and immunosuppressive medications with appropriate safety profiles in pregnancy have more favorable outcomes. However, the risk for hypertensive disorders of pregnancy, preterm birth, IUFD, low birth weight, and SGA are still a challenge in this population of women who have a history of a renal transplant. Immunosuppressive regimens continue to evolve, and counseling for childbearing, family planning, and contraception is a pertinent part of the transplant counseling process that should start prior to a kidney transplant. A multidisciplinary approach can improve outcomes and overall care.

11. Summarize the effects of pregnancy on diabetic retinopathy.

The metabolic, hypercoagulable, cardiovascular, immunologic, and hormonal changes, including a multitude of growth factors of pregnancy, can cause the development and progression of retinopathy, regardless of glycemic control. Women with longer duration of diabetes, T1D, suboptimal glycemic control, and pregnancies complicated by hypertensive disorders of pregnancy have higher risk for development or progression of their retinopathy. Therefore women with preexisting diabetes, particularly with proliferative retinopathy, are recommended to receive treatment and achieve stabilization of their retinopathy prior to conception. It is recommended by the American Academy of Ophthalmology and ADA that women with both T1D and T2D should have a dilated eye exam preconception or in the first trimester, and the frequency of follow-up visits depends on the severity of disease and risk of vision loss. Nonproliferative retinopathy generally remains stable during pregnancy but should also be followed throughout gestation as indicated by the degree of retinopathy because of the potential of progression.

12. Discuss the metabolic changes in the first trimester of pregnancy and the implications for diabetes care.

After fertilization but prior to implantation, pyruvate is the central energy substrate, but other sources, including amino acids, lactate and triglyceride-derived fatty acids, also serve numerous metabolic roles. With blastocyst formation and entry into the intrauterine cavity, there is a metabolic switch with a sharp increase in glycolysis, which parallels a rapid rise in metabolic activity at implantation.

Early pregnancy is an anabolic state, fostering nutrient storage in preparation for greater fetal demands in later gestation and lactation. Insulin secretory responses rise markedly in early pregnancy compared to the nonpregnant state, independent of changes in insulin sensitivity. In the setting of normal insulin sensitivity, a rise in first- and second-phase insulin secretion, cortisol, and leptin contribute to the increased maternal fat accretion. Between 6 to 20 weeks of pregnancy, many individuals without preexisting metabolic dysfunction demonstrate a relative increase in insulin sensitivity, attributable to an initial increase in adiponectin that subsequently falls with advancing gestation. Potential roles of adiponectin in pregnancy include its insulin sensitizing effects, influence on hepatic gluconeogenesis, lipid metabolism, and placental signaling. Metabolic changes promote lipogenesis, reduce fatty acid oxidation, and increase adipose tissue fatty acid synthesis and lipoprotein lipase, fostering maternal fat storage in early gestation. There is generally a net lipogenesis during early pregnancy among normal-weight individuals. In contrast, pregnant persons with insulin resistance predating the pregnancy have lower early gestation fat accretion and demonstrate a relative lipolysis throughout all of gestation.

In the first trimester, pregnancy-related nausea and increased insulin sensitivity may place a woman with T1D at risk for hypoglycemia and variable insulin requirements. Nocturnal hypoglycemia is particularly a risk because of the accelerated fasting state. Up to 45% of pregnant persons with T1D experience severe hypoglycemia in pregnancy, especially at night, which can be largely avoided with the use of continuous glucose monitors (CGM), insulin pumps, and antiemetic agents. A balanced bedtime snack with nutrient-dense carbohydrate, protein, and good-quality fat; routine early morning breakfast; and adjustment of overnight basal insulin dose as indicated are strategies to avoid early-morning hypoglycemia. During the first trimester, the goal is to improve glycemic control toward pregnancy glucose targets while minimizing hypoglycemic episodes to lower the risk for adverse pregnancy outcomes.

13. Describe the metabolic changes in the second and third trimesters and immediate postpartum period.

The placenta is responsible for sustaining pregnancy and facilitating a continuous supply of nutrient substrates to the fetus across gestation for normal growth and development. While maintaining euglycemia in the pregnant individual, these metabolic changes are necessary to meet the metabolic demands of the placenta and growing fetus. The fetus and placenta require glucose as the dominant fuel substrate (80%). The human fetus is dependent on a steady supply of maternal glucose until late gestation due to its limited ability for fat oxidization as an energy source and limited gluconeogenic potential. With increasing fetal–placental glucose demands in the second and third trimesters, placental-driven hormones (hPL, placental GH, cortisol, estrogen, and progesterone) and TNFα induce peripheral insulin resistance and hyperinsulinemia, leading to maternal lipolysis, increasing free fatty acid (FFA) levels, and amino acid mobilization.

There is an approximately 50% decrease in insulin-mediated glucose disposal (assessed by the hyperinsulinemic euglycemic clamp technique) and a 200% to 300% increase in insulin secretion in late pregnancy. Pregnant women with obesity enter pregnancy with increased insulin resistance, which remains persistently greater throughout pregnancy. Whether beta cells have reduced functional capacity (T2D) or are incapable of producing insulin (T1D), pregnant individuals with diabetes may require two to five times more insulin than they did before pregnancy. Fasting and postprandial hyperglycemia are risk factors for LGA, macrosomia (>4000 gm birth weight), neonatal hypoglycemia, hyperbilirubinemia, polycythemia, and long-term fetal programming of childhood and adult metabolic disease. Therefore, to achieve greater time within pregnancy-specific glucose target ranges, women with preexisting diabetes generally require multidose injections with basal and rapid-acting insulins or an insulin pump that require adjustment every 1–2 weeks with progressive insulin resistance. Pre- and postmeal glycemic monitoring provide objective assessments to safely direct insulin dosage adjustments when women cannot obtain a CGM for glycemic monitoring.

Pregnant individuals transition from carbohydrate to fat metabolism earlier (<12 hrs) in the fasting state compared to the nonpregnant state. These physiologic changes describe the "accelerated starvation of pregnancy," which results in increased ketogenesis. Available ketones and FFA serve as alternative fuel for the pregnant person, sparing glucose and amino acids for the placental–fetal unit, promoting starvation ketosis. Soon after delivery of the placenta, dramatic insulin sensitivity ensues, further increased with breastfeeding, resulting in a marked decrease in insulin requirements.

14. Do pregnant women with a BMI of 18–24.9 kg/m^2 have different glycemic patterns than those with a BMI ≥30 kg/m^2 in pregnancy?

In extensive reviews of glycemia patterns in normal pregnancy, mean fasting glucose levels were 72 mg/dL, 1-hr postprandial values were 109 mg/dL and 2-hr values were 99 mg/dL with a 24-hr mean glucose of 88 mg/dL, all much lower than current therapeutic targets. Even after controlling for diet, persons with obesity have higher 24-hr glycemic profiles and fasting and postprandial glucose levels in early (approximately 16 weeks) and late (approximately 28 weeks) gestation compared to pregnant women with a BMI in the normal range. Both early and late in gestation, women with obesity demonstrate higher fasting and postprandial glucose in spite of the higher insulin levels, averaging 5–10 mg/dl higher than in pregnancies with a normal range weight.

15. Is glucose the only fuel altered in normal pregnancy, and what is the role of lipids in fetal growth?

It is not standard to screen lipid profiles during pregnancy, although triglycerides should be checked in women with preexisting diabetes or known hypertriglyceridemia due to the marked increase in pregnancy. However, the major changes in maternal lipid metabolism during gestation also play an important role in the development of fetal fat mass and growth. The relationship between maternal lipid metabolism, placental lipid transport, and fetal fat accretion and growth is not well understood. Triglycerides (TG), cholesterol, and FFAs increase across gestation, resulting in a two- to threefold increase in TG by the third trimester.

Hyperinsulinemia activates lipoprotein lipase at the surface of fat cells but also increases the synthesis of fatty-acid-binding proteins in adipose tissue. There is increased flux of FFA into and out of the adipose tissue, and excess adiposity antagonizes insulin action and further increases insulin resistance in fat cells. Persons with obesity have higher FFA and both fasting and postprandial TGs during early and late pregnancy. TG can be hydrolyzed by placental lipases to FFAs, and maternal TG, FFAs, and placental lipoprotein lipase activity are associated with higher rates of LGA infants and increased newborn adiposity, independent obesity, and excessive gestational weight gain. Infant adiposity is associated with long-term risks for dysmetabolism and obesity. Prior studies suggest the 1-hr or 2-hr postprandial TG in early pregnancy (16 weeks) are strongly associated with infant adiposity among obese pregnant women. In contrast, in normal-weight pregnant women, a higher rise in TG from early to late pregnancy is associated with infant adiposity. Ongoing studies are exploring the role of TG in fetal overgrowth in overweight/obesity and if they should be targeted for therapy.

Amino acids are essential for protein synthesis, cell signaling, and normal fetal development. There are over 20 different amino acid transporters identified in the placenta. Amino acid transport across the placenta is maintained by a tightly regulated relationship between cumulative transporters, exchangers, and facilitators, which can be influenced by various conditions such as hypoxia and catabolic stress states. The contribution of maternal amino acids to fetal growth and fat accretion is recognized, but controlled studies are needed in normal-weight, obese, and GDM populations to determine the influence of amino acids in fetal growth and composition.

16. What are the glycemic goals in pregnancy?

Maintenance of glucose control (63–140 mg/dL) plays a significant role in reducing perinatal complications including congenital anomalies, spontaneous abortions, IUFD, macrosomia, LGA infants, neonatal metabolic abnormalities, neonatal intensive care unit admissions, and long-term offspring programming of adult diseases such as obesity, cardiovascular disease, stroke, and diabetes. The optimal glycemic levels in pregnancy to prevent adverse outcomes are unknown. The current ADA and ACOG recommendations for glycemic targets include fasting <95 mg/dL, 1-hr postprandial <140 mg/dL and 2-hr postprandial of <120 mg/dL. The results from the multicenter HAPO trial (Hyperglycemia and Adverse Pregnancy Outcomes), which studied 25,000 pregnant women in nine countries, suggest that abnormal fetal growth occurs along a continuum and at lower glucose values than previously recognized. However, more intensive goals have not been evaluated in an adequately powered RCT to determine whether they can achieve a reduction in macrosomia without increasing the risk of SGA or other adverse perinatal outcomes, especially among women with T1D who have risks for more severe hypoglycemia and growth restriction from concomitant hypertension, microvascular disease and abnormal placental development. Because LGA and macrosomia are related to both fasting glucose and postprandial glucose excursions, pregnant individuals with diabetes are recommended to monitor at least fasting and postprandial glycemia but benefit from monitoring premeal as well as postprandial glucose values to direct pharmacotherapy.

17. Why is glucose control important prior to and early in pregnancy?

Preexisting diabetes is a known risk factor for congenital anomalies, particularly involving the cardiovascular, central nervous, and genitourinary systems. However, compared to infants born to mothers without diabetes, pregnancies complicated by GDM also have a greater risk for an infant to be born with congenital anomalies (adjusted RR 1.28; 95% CI 1.24–1.31).

Congenital malformations are the leading cause of infant death, and etiologies are often multifactorial. Diabetes and hyperglycemia adversely affect yolk sac nutrient transport, morphology, and vasculopathy. Molecular pathways suggested to contribute to these pathologies are (1) GLUT2-mediated high rates of glucose transport into the embryo during hyperglycemia; (2) hyperglycemia-induced oxidative stress-mediated abnormalities; (3) down regulation of hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF) that are important regulators of angiogenic factors; and (4) inhibition of *Pax3* expression and activation of apoptosis signal-regulating kinase 1 (ASK1), which both promote apoptosis.

Anomalies associated with diabetes commonly occur before the 8th week of gestation. The most common fetal anomalies include cardiovascular, neurologic, or urogenital systems but have been shown to be associated with all subtypes of fetal malformations. The neural tube is completely formed by 4 weeks and the heart by 6 weeks after conception, underscoring the critical importance of preconception glycemic control. Although there is no single syndrome specific to diabetes, caudal dysgenesis syndrome (i.e., caudal regression or sacral agenesis) is a rare condition seen with diabetes and characterized by maldevelopment of the caudal portion of the body with variable degrees of genitourinary, skeletal, gastrointestinal and limb defects.

18. Describe the utility of measuring an early pregnancy HbA1c.

HbA1c is a glycemic metric that represents the average glucose exposure over a red blood cell turnover cycle (approximately 3 months). Therefore it does not reflect glycemic patterns or variability and does not capture the severity of hypoglycemia and hyperglycemia. During pregnancy, HbA1c should not be used to direct medical management and therapeutic changes but can be useful as a counseling tool for perinatal risks associated with glycemia. Although it reflects overall glycemic control over 3 months, it often does not capture glycemic control over the shorter course of organogenesis (approximately 5 weeks) and lacks precision in predicting major anomaly risk. Because of the increased plasma volume, increased erythrocyte cell turnover during pregnancy, and increased triglycerides with advancing gestation, HbA1c is lowered approximately 0.5–0.8% by pregnancy alone. It is generally recommended that women desiring a future pregnancy aim for a preconception HbA1c goal of <6.5% if it can be achieved safely.

The general population prevalence of congenital anomalies is 2–3%. Periconception HbA1c is used as a surrogate marker for glycemic control; prior studies have demonstrated a somewhat linear relationship between the periconception HbA1c level and the risk of hyperglycemia-induced anomalies (i.e., diabetic embryopathy) with risks as high as 25% with HbA1c levels >12–13%. The relative risk reduction for congenital malformations for each 1% decrease in HbA1c has been reported to be between 0.39 and 0.59, achieving risks similar to population-based levels with HbA1c <6%.

19. Why is glucose control important later in pregnancy?

In late gestation, women with T1D and T2D have a three- to fivefold increased risk of stillbirth and perinatal deaths compared to the general population, especially when diabetes is complicated by obesity, suboptimal glycemic control, hypertension, or renal and vascular disease. Often unrecognized, pregnancies complicated by T2D have an even higher risk for IUFD than those in women with T1D, and this risk is also significant with insulin-requiring GDM, particularly when additional morbidities such as higher age, increased body mass index, OSA, and preeclampsia are present. Progressively higher HbA1c correlates with higher rates of LGA, preeclampsia, fetal growth restriction, neonatal hypoglycemia, preterm birth, and stillbirth. Notably, the combination of Class 3 obesity and preexisting diabetes (T1D or T2D) has been shown to increase the stillbirth risk by approximately 30-fold at term, likely due to fetal overgrowth, placental insufficiency, and fetal ischemia near term.

The regulation of fetal nutrients, particularly in the setting of diabetes, is not well characterized. Increased maternal availability of substrates such as glucose, amino acids, FFA, and triglycerides allows the potential for greater placental transport to the fetus, resulting in fetal overgrowth and fat accretion. Glucose is transported via facilitated diffusion across the placenta. Therefore the glucose concentration difference between the maternal and fetal compartments drives the flux of glucose to the fetus. Hyperglycemia results in fetal pancreatic islet hypertrophy and beta-cell hyperplasia with consequent fetal hyperinsulinemia, which is a potent growth stimulator. Therefore maternal hyperglycemia and fetal hyperinsulinemia, which may occur by 14 weeks' gestation, contribute to the increased glucose transfer to the fetus. Hyperglycemia also plays a role in lung surfactant synthesis, increasing the risk for respiratory distress syndrome (RDS) and other transient respiratory conditions.

Amniotic fetal insulin levels, a marker of fetal hyperinsulinemia, correlates strongly with the fetal abdominal circumference at 28–32 weeks. Insulin is an anabolic hormone that stimulates the fetal mitogenic and anabolic pathways in the developing fetal organs including skeletal muscle, liver, and adipose tissue. Moreover, fetal growth and development are dependent on other growth factors such as glucose, placental GH, insulin-like growth factor-1 and insulin-like growth factor binding protein 1, and adiponectin, but the role of these alterations on fetal growth, principally in the setting of diabetes, is not well understood.

The placenta plays a key role in the regulation of nutrient transport in pregnancy. Glucose and amino acids are critical for the development of the fetus, but transfer of lipids to the fetal compartment is important for cellular and brain development, fat accretion, and overall fetal growth. The placental transport mechanism for lipids is complex and remains poorly understood. Diabetes, including GDM, is associated with dysregulated maternal lipid metabolism, decreased placental fatty acid oxidation, increased inflammatory cytokines, and differentially methylated genes involved in energy and lipid metabolism, which can influence fetal fat accretion and growth. Increased fat availability to the fetus leads to adiposity and visceromegaly (especially heart, liver, and pancreas), which can increase fetal abdominal girth disproportionate to other body measurements (body-to-head disproportion), increasing the risk for Cesarean delivery. These early metabolic changes in the offspring place it at risk for immediate complications such as shoulder dystocia and potential birth trauma but also future metabolic disease and obesity.

The placenta plays a vital role in fetal health, growth, and development. Hyperglycemia, diabetes, and obesity have been associated with placental dysfunction. Molecular processes found to be potentially contributing are decreased trophoblast mitochondrial activity, altered pathways mediating reactive oxygen species, glucose toxicity and lipotoxicity, and abnormal villous tree formation. Depending on the degree of placental dysfunction and gestational age, pregnant women with diabetes also have higher risks for FGR, SGA, and low birth weight, especially in those with microvascular disease, hypertension, proteinuria, and renal dysfunction.

20. Summarize the risks to the pregnant person with diabetes.

- Women with preexisting diabetes have higher risks for diabetic ketoacidosis (DKA) occurring at lower glucose levels (<200 mg/dl) and hyperosmolar hyperglycemic syndrome (HHS).
- Women with T1D have higher risks for developing hypoglycemia, especially nocturnal hypoglycemia, and hypoglycemic unawareness, particularly in the first 16 weeks of pregnancy.
- Women with diabetes have an increased risk for progression of retinopathy, proteinuria, and nephropathy, especially if renal dysfunction is already advanced.
- The immediate risks to the pregnant person with diabetes include an increased incidence of cesarean delivery, preeclampsia, higher-order perineal lacerations, postpartum hemorrhage, and polyhydramnios, which can result in preterm labor.
- The long-term risks to pregnant individuals with GDM are recurrent GDM in future pregnancies (30–50% recurrence), with progression to T2D (33–74%) within 10 years and cardiovascular disease. Risk factors for progression to T2D include fasting hyperglycemia, pharmacotherapy requirement for managing glycemia, GDM diagnosed <24 weeks of gestation (preexisting glucose intolerance), obesity, FH of T2D, ethnicity associated with T2D risk, multiple subsequent pregnancies, postpartum weight retention, and impaired glucose tolerance or impaired fasting glucose (prediabetes) at 6 weeks postpartum.

21. Summarize the risks of infants born to pregnant women with diabetes.

- T1D and T2D, especially if poorly controlled, are associated with higher risks for perinatal death (i.e., spontaneous abortions, IUFD, and neonatal deaths)
- Fetal cardiac septal hypertrophy has been demonstrated in 35–40% of pregnancies with diabetes, including GDM.
- Diabetes is an independent risk for abnormal offspring growth, including macrosomia (≥4000 g birth weight), LGA (≥90th percentile for gestational age), or SGA (<10th percentile for gestational age), especially when associated with placental insufficiency. Excess FFA and TG delivered to the fetus may also contribute to excess fetal growth and is a subject of investigation.

- Shoulder dystocia and birth injury (Erb's or Klumpke's palsy, Horner's syndrome, clavicular fracture, facial nerve palsy, cephalohematoma) are increased, especially with fetal overgrowth.
- Babies have higher NICU admission rates due to neonatal hypoglycemia, hyperbilirubinemia, polycythemia, feeding difficulties, and consequences of prematurity including respiratory distress. Even in GDM, the incidence of individual neonatal complications ranges from 12% to 28%, which is higher than pregnancies that are not complicated by GDM.
- Long-term infant programming effects of hyperglycemia and hyperlipidemia include childhood obesity, T2D, cardiovascular disease and neurobehavioral disorders with possible effects on appetite regulation and CNS pathways involving serotonin and dopamine.
- Proliferation of fetal adipocytes and pancreatic beta cells may be responsible for "fetal programming" the later development of obesity and metabolic syndrome in addition to changes in appetite regulation, mitochondrial capacity, and adipogenic potential of stem cells. Interestingly, newborns from obese GDM women already have 68% more intrahepatic fat by Magnetic Resonance Imaging/Magnetic Resonance Spectroscopy (MRI/MRS) than newborns from normal-weight mothers, possibly serving as a "first hit" to increase their risk for developing nonalcoholic fatty liver disease. Further human and nonhuman primate studies are needed to determine the contributions of epigenetic disturbances with metabolic function and long-term developmental programming consequences.

22. What are the maternal/fetal risks of severe hypoglycemia?

In sheep, chronic hypoglycemia reduces basal and glucose-induced fetal insulin secretion and increases net protein breakdown. In the human fetus, maturation of hepatic gluconeogenesis does not occur until close to delivery. Whether severe and prolonged hypoglycemia or wide fluctuations of severe hyper- and hypoglycemia could have long-term adverse neurological effects in the offspring is unknown.

For overall safety, pregnant persons should minimize hypoglycemic episodes to reduce progression of hypoglycemic unawareness, the risk of hypoglycemic seizures, risk of trauma, and the psychological stress of being hypoglycemic. Maternal hypoglycemia has declined with the advancing CGM technology, insulin pump devices, and hybrid closed-loop insulin therapies. If CGM is not used, monitoring in the middle of the night is recommended among women with T1D because of the increased risk of nocturnal hypoglycemia, especially with hypoglycemia unawareness.

Pregnant women with T1D have higher risks for hypoglycemia during the first and early second trimesters due to the relative insulin sensitivity during this period and diminished counterregulatory hormonal responses to hypoglycemia in pregnancy. After delivery of the placenta, postpartum insulin requirements decrease dramatically to less than prepregnancy levels or a 60–70% reduction from third-trimester requirements. Additionally, the counterregulatory effect of pituitary GH is transiently suppressed by placental GH. During the first 2–4 weeks postpartum, many women who are breastfeeding experience greater episodes of hypoglycemia, which may be secondary to slightly greater insulin sensitivity, a modest increase in caloric requirements, and/or inconsistent carbohydrate intake during this life transitioning period.

23. What is the role of continuous glucose monitoring (CGM) in pregnancy?

The CONCEPTT trial demonstrated modest improvements in HbA1c and glucose time in range (TIR) of 63–140 mg/dl) but highly significant improvements in neonatal outcomes (LGA and NICU admissions) among participants with T1D that used CGM during pregnancy compared to those who did self-monitoring of blood glucose (SMBG) alone. Mean glucose, glycemic variability, nocturnal glucose, and fasting glucose have also been associated with important perinatal outcomes and it is unclear whether the optimal nocturnal TIR should be different than the daytime TIR. An international panel at the 2019 Advanced Technologies & Treatments for Diabetes Congress made recommendations on the clinical targets for CGM. The recommended goals for pregnant women with T1D include 70% glucose TIR (63–140 mg/dL), <4% time-below-range (<63 mg/dL), and <25% time-above-range (>140 mg/dL). However, targeting glucose levels as low as 63 mg/dl with insulin in women with T1D, especially if they have hypoglycemic unawareness, may increase the risk of hypoglycemia. Therefore some experts recommend targeting a range of 70–140 mg/dl and treatment of maternal glucose levels <70 mg/dL in T1D. The ADA recommends CGM use in addition to SMBG in T1D to reduce LGA and neonatal hypoglycemia. There is insufficient evidence to direct CGM targets for pregnant women with GDM or T2D and there is no compelling data at this time that CGM improves outcomes compared to SMBG alone. Trials are underway and it is likely that more stringent targets will be required to normalize perinatal outcomes.

24. Discuss the role of the insulin pump during pregnancy.

Metabolic homeostasis is influenced by many factors including sleep, stress, exercise, nutrition, and circadian rhythm. The dynamic physiologic changes of pregnancy (rising insulin resistance and lipids, changes in weight, sleep disruptions) add to the challenges of maintaining metabolic homeostasis. Therefore insulin pumps are advantageous to allow for more control and adaptability throughout the day and across gestation, constantly responding to the changing metabolic demands. Insulin pump therapy may be especially helpful for women who have T1D and are insulin sensitive and have variable insulin requirements through the night.

DKA can occur rapidly in women who are on multiple daily insulin injections (MDI) or who experience pump failure during pregnancy due to the short activity of rapid-acting insulin. Additionally, there are unique problems with infusion sites during pregnancy. Because pump failures place pregnant women at significant risk for DKA and consequential adverse pregnancy outcomes, insulin pump therapy is not ideal for all women. Due to the steep learning curve of using pump therapy, initiation of pump technology for diabetes management is recommended prior to pregnancy. Currently, there are no RCTs demonstrating that pump therapy is superior to MDI use in pregnancy. It has been demonstrated that with the increasing insulin resistance of pregnancy and higher insulin requirements, prebolusing before meals by at least 15 minutes in early pregnancy and up to 45 minutes in later pregnancy is usually necessary to match insulin and glucose peaks.

Despite significant improvements in insulin therapies, CGM, and insulin pump devices, the majority of pregnant persons with preexisting diabetes have difficulty achieving pregnancy glucose targets (63–140 mg/dL). There are currently no US marketed sensor-integrated automated insulin delivery systems (hybrid closed loop; HCL) approved in pregnancy and none have algorithms to achieve the lower pregnancy targets. However, a multicenter randomized trial in England, Ireland, and Scotland (AiDAPT; n=124) demonstrated that participants with T1D randomized to a pregnancy-specific HCL system (CamAPS FX application) achieved greater TIR (63–140 mg/dL). The mean adjusted difference in the percent TIR between the groups over the course of the treatment period was 10.5%; 95% CI 7.0–14.0; $P < 0.001$). Participants on HCL also spent less time with glucose levels above the target range (>140 mg/dL) than those assigned to the standard-care group (MDI) or sensor-augmented pump therapy (mean difference, −10.2%) without additional hypoglycemic episodes. The use of HCL pumps in pregnancy is an area of intensive and ongoing investigation. If it is judged that an individual's glycemic control is superior on HCL than on sensor-augmented pump therapy or MDI, continuation of the HCL is reasonable, especially if adjustments to basal rates, carb ratios, and correction factors are enabled throughout the course of pregnancy.

Continuation of pump therapy at delivery may be reasonable if an elective Cesarean delivery is planned. However, insulin requirements may change throughout active labor so an intravenous insulin infusion may be a safer alternative for women who plan to labor. Programming a postpartum insulin regimen to be immediately switched to after delivery is of paramount importance to avoid severe postpartum hypoglycemia given the marked decrease in insulin requirements that occurs abruptly after delivery. Some pumps using retrospective insulin algorithms based on recent third-trimester higher insulin requirements may need to be reset and switched to manual mode immediately for the first postpartum week.

25. What is the risk of diabetic ketoacidosis (DKA) in pregnancy?

DKA may occur at lower glucose levels (often referred to as "euglycemic DKA") because of the decreased buffering capacity in pregnancy (i.e., respiratory alkalosis with compensatory metabolic acidosis), increased glomerular glucose filtration, continuous glucose utilization by the fetal-placental unit, and increased plasma volume. An early switch from carbohydrate metabolism to lipolysis occurs in pregnant women who have depleted their glycogen stores after a 10–12 hr fast, resulting in starvation ketosis.

Pregnant women with T1D who are unable to keep down food or fluids or have persistent severe hyperglycemia should check urine ketones at home frequently. If urine ketones cannot be cleared quickly, a chemistry panel should be ordered to rule out an increased anion gap, regardless of the glycemic status. A common precipitant for DKA in pregnancy is nausea and vomiting, but other causes such as urinary tract infections should be aggressively investigated. Pregnant individuals with T2D or GDM requiring insulin can also develop DKA or hyperglycemic hyperosmolar syndrome, especially in the context of prolonged fasting, infections, or corticosteroid administration for fetal benefit. All women with diabetes in pregnancy should be counseled on the signs and symptoms of DKA.

26. How does maternal DKA affect the fetus?

Rates of stillbirth after a DKA episode are high (15%). Women who develop DKA in pregnancy are more likely to have hypertensive disorders of pregnancy, preterm birth, stillbirth, and NICU admissions. Risk factors for fetal loss include maternal ICU admission, later gestation, delayed treatment and higher serum osmolality during DKA. Early identification and treatment of any maternal inciting conditions, abnormal glycemia, acid/base abnormalities, and volume deficit is necessary to improve fetal status. Without adequate oral carbohydrates, fat will be burned for fuel and the woman with DKA will remain ketotic. Those unable to reliably consume oral nutrients should be given intravenous glucose and D10 glucose solutions to meet the 175–220-gm carbohydrate demands of the fetal-placental unit in the third trimester to reverse ketosis.

27. What is the role of sleep in diabetes and pregnancy outcomes?

Adequate sleep duration and quality are important for normal physiologic functions, metabolic and appetite regulation, and hormone processes. Physiologic and anatomic changes with advancing gestation during pregnancy can contribute to altered sleep quality compared to nonpregnant individuals (reduction of slow-wave-sleep, increasing cortisol, changes in respiratory capacity, and increased nocturia). Disturbances in sleep duration and quality have long been associated with carbohydrate metabolism, cardiovascular function, and appetite control.

Sleep- disordered breathing (SDB) encompasses a spectrum that ranges from mild to complete obstruction of airflow; furthermore, the etiology of the disruption can also be variable (central, obstructive, and mixed events). Prepregnancy obesity and higher weight gain are associated with increased risks for the development and worsening of SDB, including obstructive sleep apnea (OSA). Rates of at least mild OSA have been reported to be between 15–67% in pregnancy and are associated with higher glycemic patterns by CGM, more hepatic insulin resistance, and higher cortisol levels. OSA is also associated with oxidative stress, pulmonary hypertension, and in severe cases, right heart failure. SDB and shorter sleep duration are also significantly associated with increased rates of GDM and preeclampsia, higher glycemic patterns, an increased inflammatory response, oxidative stress, and impaired glucose tolerance and insulin resistance. Moreover, SDB has been correlated with both growth restriction, possibly due to placental ischemia, and LGA infants, suggesting the potential developmental programming influence of altered sleep during pregnancy on future long-term offspring health. Due to the potential for consequential adverse effects on both mother and the fetus, SDB should be identified and treated preconception or certainly during early pregnancy in individuals with obesity or metabolic disease.

28. What is the relationship between depression and diabetes?

One in 10 women suffer from symptoms of depression in the United States, but this likely underestimates the true prevalence. Pregnant women are challenged with dramatic physiological, anatomical, and emotional changes throughout pregnancy and transitioning to a new life following delivery. A GDM diagnosis complicates the psychosocial disturbances of a "normal" pregnancy. Moreover, women with diabetes often are faced with diabetes distress and psychological factors that can impact self-care and consequently perinatal outcomes. Among pregnant women with diabetes, untreated antenatal anxiety and depression are associated with higher rates of preterm birth and hypertensive disorders of pregnancy. Pregnancies complicated by any subtype of diabetes have higher rates of antenatal and postpartum depression. Moderate to severe anxiety and depression treated with medications such as SSRIs are associated with better outcomes for both mother and child than when untreated. Further studies are needed to determine optimal treatment in pregnancy to improve perinatal and offspring outcomes. Identification and appropriate treatment benefits not only the mother but improves both short-term and long-term offspring outcomes.

TABLE 8.1 Carpenter and Coustan Criteria for a Positive 100 gm Oral Glucose Tolerance Test

Fasting glucose	≥95 mg/dL
1-hr glucose	≥180 mg/dL
2-hr glucose	≥155 mg/dL
3-hr glucose	≥140 mg/dL
***2 abnormal values needed**	
IADPSG Criteria for a Positive 75 gm Oral Glucose Tolerance Test	
Fasting glucose	≥92 mg/dL
1-hr glucose	≥180 mg/dL
2-hr glucose	≥153 mg/dL
***1 abnormal value needed**	
Overt Diabetes	
Fasting glucose	≥125 mg/dL
HbA1c	≥6.5%
2-hr (75 gm)	≥200 mg/dL
Random glucose	≥200 mg/dL
***Any of above**	

29. What is gestational diabetes mellitus (GDM) and how is it diagnosed?

ACOG defines GDM as a “condition in which carbohydrate intolerance develops during pregnancy” and is a type of diabetes that is recognized during pregnancy that does not meet criteria for T1D, T2D, monogenic, or other disease conditions associated with diabetes. It is associated with increased adverse perinatal outcomes, maternal progression to T2D and CVD, and long-term risks for cardiometabolic disease in the offspring. All pregnant persons are recommended to undergo glucose testing between 24 and 28 weeks to screen for GDM with either the one-step or two-step approach. There is a lack of consensus regarding early screening in high-risk individuals but recent data favors that approach.

TWO-STEP APPROACH

Prior to 2010, the two-step approach for GDM testing was universally advocated in the United States A screening 50-gm 1-hr oral glucose challenge test (OGCT) is first performed. If the glucose response is ≥200 mg/dL and a FBG is ≥95 mg/dl, a 3-hr oral glucose tolerance test (OGTT) can be avoided and the woman is diagnosed with GDM. If the 50-gm glucose response is greater than the institutional threshold (≥130–140 mg/dL) but below 200 mg/dL, a 100-gm 3-hr fasting OGTT is performed. The sensitivity and specificity of the 50-gm screening test depends on what threshold value is chosen by an institution, commonly selected according to the population prevalence of GDM in the region. GDM is diagnosed if ***two*** of four values on the 100-gm 3-hr OGTT are elevated (Table 8.2).

The 100-gm 3-hr OGTT diagnostic thresholds to diagnose GDM were actually based on the future risk of developing diabetes *after* pregnancy and not on adverse outcomes during pregnancy. The test should be performed after 3 days of unrestricted carbohydrate consumption and while fasting for at least 8 hrs. Several studies have suggested increased adverse outcomes with only one abnormal value on the 3-hr OGTT that are similar to pregnancies complicated by GDM, but further studies are necessary to determine if this population would benefit from treatment. If only one value is elevated on the 100-gm 3-hr OGTT test, a repeat 100-gm 3-hr test should be considered 3–4 weeks later, as one-third of these women will ultimately meet the diagnostic criteria for GDM (Table 8.1).

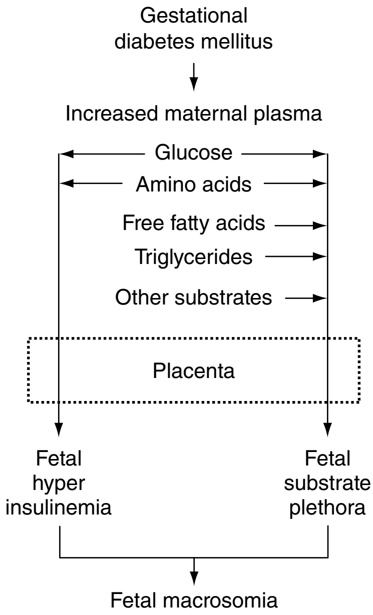

Fig. 8.1 Macronutrient Contributors to Fetal Macrosomia.

ONE-STEP APPROACH

For the first time, the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) trial in 25,000 women in multiple countries demonstrated a continuous association of maternal glucose levels and adverse pregnancy outcomes (LGA, elevated cord C-peptide [marker of fetal hyperinsulinemia], primary cesarean deliveries, and neonatal hypoglycemia) on a 75-gm OGTT at glucose values lower than historically appreciated to be associated with perinatal complications. Based on these findings, the International Association of Diabetes in Pregnancy Study Group (IADPSG) developed GDM criteria using a ***single*** abnormal threshold glucose value on a 75-gm 2-hr OGTT to predict a 1.75-fold increased risk in LGA. This threshold identifies individuals at risk for adverse perinatal outcomes by approximately 2–3 times more than the 100-gm OGTT.

A NIH Consensus Development Conference on diagnosing GDM in 2013 reviewed the existing literature at that time. They concluded that adopting the IADPSG (one-step approach) would "increase the prevalence of GDM by approximately threefold and the corresponding costs and interventions without clear demonstration of improvements in the most clinically important health and woman-centered outcomes." Numerous trials have been done comparing the two diagnostic tests and overall concluded that similar pregnancy outcomes are achieved with either, demonstrating that different strategies to *identify* an at-risk population alone may not improve perinatal outcomes. WHO has adopted the one-step approach, ACOG continues to support the two-step approach, and the ADA supports either; this has left providers to choose to use one diagnostic criteria over the other, resulting in a lack of standardization clinically and in research trials.

30. Early screening for diabetes or GDM.

ACOG, ADA, Endocrine Society, and USPSTF support universal GDM testing at 24–28 weeks' gestation. With the increasing prevalence of people with obesity, delayed childbearing, and nearly a quarter of the population with potentially undiagnosed diabetes or prediabetes, there is concern that women may present to pregnancy with undiagnosed preexisting diabetes. Pregnant women with T2D or evidence of hyperglycemia in early pregnancy have a much higher risk of maternal and fetal complications, including major malformations (if HbA1c is ≥6.5%), spontaneous abortions, hypertensive disorders of pregnancy and LGA. Therefore the IADPSG, WHO, ADA,

TABLE 8.2 ADA and ACOG Risk Factors for Screening for Diabetes and GDM

1. *Early* testing should be considered in overweight or obese (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans) adults who have one or more of the following risk factors:
    - First-degree relative with diabetes
    - High-risk race/ethnicity (e.g., Black, Latino, Native American, Asian American, Pacific Islander)
    - History of CVD
    - Hypertension (≥130/80 mmHg or on therapy for hypertension)
    - HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
    - Women with polycystic ovary syndrome
    - Physical inactivity
    - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. ADA recommends measuring A1C in all women, preconception or before 15 weeks to diagnose preexisting diabetes. ADA recommends screening high-risk individuals for abnormal glucose metabolism using a FBG of 110–125 mg/dl or A1C 5.9–6.4% before 15 weeks.
3. Women with prediabetes (A1c ≥5.7%, IGT, or IFG) should be tested yearly.
4. Women who were diagnosed with GDM should have lifelong testing at least every 3 years with consideration of annually depending on risk status.

and ACOG recommend early testing to rule out T2D with the initiation of prenatal care among individuals at high risk for diabetes (Table 8.2).

The ADA recommends that if individuals are not screened prior to pregnancy, universal early screening at <15 weeks for undiagnosed diabetes may be considered over selective screening. GDM is diagnosed if glucose intolerance was identified during pregnancy AND women do not meet diagnostic criteria for overt (preexisting) diabetes (A1C ≥6.5%, fasting plasma glucose >125 mg/dl, or random plasma glucose ≥200 mg/dl). There are data that early abnormal glucose metabolism, defined as a fasting glucose threshold of 110 mg/dl or an A1C of 5.9% (typically associated with prediabetes) may identify individuals who are at higher risk of adverse pregnancy and neonatal outcomes, are more likely to need insulin treatment, and are at high risk of a later GDM diagnosis.

The fetus can secrete insulin in response to maternal hyperglycemia at 12–14 weeks. Because there is evidence that individuals who already demonstrate glucose intolerance early in pregnancy at the level of prediabetes may have similar outcomes as those with pregnancies complicated by preexisting diabetes, studies are underway attempting to develop outcome-based criteria for the diagnosis of “early” GDM. Prior studies including one RCT using the current 2-step approach for early diagnosis of GDM demonstrated no difference in perinatal outcomes. However, the major limitation of the study was that the average gestational age in the early screening group was 24.3 ± 5.2 weeks compared to 27.1 ± 1.7 weeks in the routine screen group, a 3-week mean difference which was not significantly earlier. Simmons et al. performed a RCT using the 1-step diagnostic criteria for GDM diagnosis at approximately 15.6 weeks and demonstrated a modest decrease in adverse neonatal events compared to conventional screening and treatment (24.9% versus 30.5%; $P = .2$), suggesting a potential benefit in individuals who have screening and treatment initiation at <14 weeks.

Profound differences in the sensitivity of a FBG versus a 1-hr or 2-hr 75-gm glucose value in diagnosing GDM have been demonstrated among different ethnic populations. One major drawback of the 2-step method in Latino or Hispanic populations, is that the 50-gm screen may miss fasting hyperglycemia and this population has been shown to predominantly have elevated FBG due to hepatic insulin resistance and increased gluconeogenesis. In these individuals, it may be important to add a FBG to a glucose screening test given fasting hyperglycemia has been shown to be a major risk factor for fetal overgrowth, but ACOG guidelines have not made recommendations about screening in these populations. It must also be recognized that the HbA1c does not have the sensitivity nor specificity to diagnose GDM and women should be advised to follow up with an OGTT.

31. What is the etiology of GDM?

GDM is caused by abnormalities in at least three aspects of fuel metabolism: insulin resistance in fat and muscle, increased hepatic glucose production, and impaired insulin secretion. Although insulin levels may be high, the increased insulin resistance of pregnancy still results in inadequate compensation because impaired beta-cell function leads to insufficient insulin secretion to maintain euglycemia in the presence of severe insulin resistance. The insulin resistance is thought to be due to increased production of hPL, placental GH, TNFα, and inflammatory cytokines. Women who develop GDM have lower pregravid insulin sensitivity compared with matched control groups. Many individuals who develop GDM have characteristics of metabolic syndrome before pregnancy (higher BMI, lipid abnormalities, greater waist circumference, hypertension, etc.). Women who do not have an elevated BMI or have dysmetabolic phenotypes but are found to have GDM may represent a higher-risk group for future cardiometabolic disease or are misdiagnosed and have autoimmune diabetes or genetic types of diabetes such as monogenic diabetes.

A small percentage of women diagnosed with GDM may display features of LADA (latent autoimmune diabetes in adults) or monogenic diabetes, that is, MODY (maturity onset diabetes of the young), most commonly MODY-2. Thus, a strong family history, especially of diabetes in family members who were not overweight, is important. Genetic testing for MODY should be offered since the fetus has a 50% risk of transmission. Women with LADA often are unable to control their glucose with nutrition and lifestyle modifications secondary to the increased insulin requirements of pregnancy resulting in hyperglycemia. They may be diagnosed for the first time in pregnancy or postpartum and may present in DKA. When LADA is suspected, testing for glutamic acid decarboxylase (GAD65) antibodies, antiZnT8 antibodies, and IA-2 antibodies may be appropriate.

32. What is the white classification of diabetes in pregnancy?

In 1949, Priscilla White at the Joslin Clinic developed a classification scheme for fetal and maternal pregnancy risks based on the prepregnancy state in women with T1D. She observed that the woman's age at onset and duration of diabetes (Classes B-D), and severity of diabetes-related complications, including vascular disease, nephropathy (F), and retinopathy (R), significantly influenced maternal and perinatal outcomes. Since the current diabetes classifications were adopted in the late 1990s to define T1D and T2D by cause rather than by treatment, the White Classification has been less commonly used by obstetricians to classify the duration and complications of women with diabetes. Class A1 (nutrition and lifestyle management) and (oral or injectable interventions) subpopulations of GDM continue to be used in practice today.

33. What is the role of exercise in women with GDM or preexisting diabetes?

Pregnancy is a motivating period to adopt healthy habits and behaviors for fetal benefit. All women should be encouraged to continue or begin both cardiovascular and resistance activity during pregnancy. ACOG, ADA and American Heart Association support the *Physical Activity Guidelines for Americans, 2nd edition* recommendations for a goal of 20 minutes daily of cardiovascular effort (150 minutes per week of moderate-intensity aerobic activity) and 2–3 days per week of resistance activity as long as there is not an obstetric contraindication. Moderate exercise is well tolerated and safe in pregnancy, and some data suggest improved placentation. Exercise may improve postprandial excursions and fasting glycemia, excessive weight gain, and adverse perinatal outcomes such as cesarean delivery and macrosomia. Some women with mild postprandial hyperglycemia may be able to avoid insulin therapy by adding aerobic or resistance exercise after eating. Women who exercise prior to pregnancy can safely continue exercise during pregnancy and through the postpartum period. Exercise alone initiated in the second half of pregnancy without changes in nutrition has not been shown to decrease rates of GDM but may be associated with favorable outcomes.

34. When is an exercise program contraindicated?

Some absolute contraindications for exercise that were previously reported have recently been questioned; therefore providers should individualize exercise prescriptions. Absolute contraindications include hemodynamically significant heart disease, restrictive lung disease, incompetent cervix, persistent second- or third-trimester bleeding, active premature labor, severe preeclampsia, and severe anemia.

35. What is the best nutritional intervention for pregnant women with diabetes?

Women with any type of diabetes should receive education and support from a nutritionist, set exercise goals with their provider, and review glycemic goals and management strategies. All pregnancies should have a healthy foundation of nutrient-dense, diverse food choices and physical exercise, which has been demonstrated to reduce gestational weight gain and lower the risk for adverse perinatal outcomes. The recommended dietary allowance (RDA) for carbohydrate intake is currently set at ≥175 gm/day or 45–65% of total energy intake to account for both maternal brain and fetal brain glucose requirements. However, recently the placental energy substrate demand to sustain a healthy pregnancy was calculated to be an additional 36 g/day, suggesting a potential greater need for daily carbohydrate consumption (approximately 210 g/day) to promote normal fetal-placental growth and development.

Medical nutrition therapy is a first-line intervention for GDM, but there is not a consensus on evidence-based nutritional recommendations for GDM. Any dietary intervention following GDM diagnosis has been shown to reduce fasting and postprandial glycemia, decrease pharmacotherapies, and lower rates of macrosomia. Traditionally, carbohydrate restriction has been the primary approach to treatment for diabetes in pregnancy, but this can increase the risk for micronutrient deficiencies and lower energy intakes. However, the Choosing Healthy Options in Carbohydrate Energy (CHOICE) RCT limited simple carbohydrates but liberalized complex carbohydrates (60% complex carbohydrates, 25% fat) and has challenged the conventional "low"-carbohydrate diet (40% carbohydrate, and 45% fat). This RCT in diet controlled GDM in which all meals were provided, simple carbs and saturated fats were limited, and total calories were controlled, demonstrated similar newborn adiposity and maternal 24-hr glycemia despite liberalizing complex carbohydrates up to a 100-gm difference when fat was proportionally reduced. However, liberalization of complex carbs to this degree while reducing fat is not recommended in women with insulin requiring GDM or preexisting diabetes, due to the need for more exogenous premeal insulin to cover a higher carbohydrate diet. Nutritional goals should be individualized in GDM and be dynamic, tailored to cultural backgrounds, lifestyle preferences, resource availability, and education; total calories must still be controlled.

36. What is the recommended weight gain during pregnancy?

Excessive weight gain in pregnancy is associated with increased adverse perinatal outcomes such as LGA. Although weight loss during pregnancy is not advocated, individuals with GDM may lose weight or maintain current weight after initiation of lifestyle interventions. Although the weight gain parameters to maximize perinatal outcomes for pregnant women with diabetes are unknown, the National Academies of Medicine (formerly Institute of Medicine) recommends gestational weight gain goals specific for each BMI category in pregnancy (BMI <18.5, 28–40 lbs.; BMI 18.5–24.9, 25–35 lbs.; BMI 25–29.9, 15–25 lbs.; BMI ≥30, 11–20 lbs.). However, the obligate weight gain in pregnancy (includes fetus, placenta, increased uterine size, breast development, amniotic fluid, and increased blood volume) is only approximately 17 lbs. and some studies suggest that women with Class 2 or Class 3 obesity may not need any significant weight gain for normal fetal growth. Given the obesity epidemic and high rate of LGA, targeting the lower weight gain ranges are usually recommended.

37. When should medical therapy be used to treat GDM?

After receiving and implementing nutritional education, working toward prescribed exercise goals, and incorporating other lifestyle behavioral modifications to prevent excess weight gain, women who are not meeting pregnancy glucose targets (FBG <95 mg/dL, 1-hr postprandial glucose, <140 mg/dL, and 2-hr postprandial glucose <than 120 mg/dL) should be started on pharmacotherapy. Insulin is the preferred pharmacologic agent. It is also appropriate to consider medical therapy when ultrasound evaluation indicates fetal growth to be consistent with LGA or the fetal abdominal circumference (AC) is >90% after 30 weeks. Pharmacotherapy should be individualized to the woman's schedule, meal timing, and characteristics of hyperglycemia, as described previously. Serious hypoglycemia is uncommon among pregnant women with GDM who receive insulin teaching.

Although insulin is the preferred agent for GDM, there is limited data on oral antidiabetic agents in pregnancy. Metformin and glyburide both cross the placenta and have limited long-term offspring safety data. Women who are unable to safely administer insulin or strongly prefer oral agents may be candidates for metformin or glyburide with individualized counseling and care.

38. Discuss the role of oral and injectable medications for the treatment of diabetes and their limitations during periconception and pregnancy.

Insulin is the first-line agent and the only FDA-cleared therapy for the treatment of diabetes in pregnancy. Several professional groups and guidelines acknowledge the off-label use of glyburide and metformin for treatment of GDM, with metformin typically being preferred over glyburide. Two RCTs have evaluated the addition of metformin to insulin in pregnant women with T2D. There are 11 subclasses of pharmacologic agents for the treatment of T2D: a biguanide (metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, a thiazolidinedione, dipeptidyl peptidase-IV inhibitors (DPP-4 inhibitors), a bile acid sequestrant, a dopamine agonist, sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors), glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA), and a combined GLP-1 plus glucose dependent insulinotropic peptide (GIP) receptor agonist (GLP-1/GIP RA). The GLP-1 RA are available in injectable and oral forms; the GLP-1/GIP RA is only available as an injectable agent. All oral and noninsulin injectable antidiabetic drugs used for the treatment of diabetes are off-label for use in pregnancy.

Oral and injectable noninsulin agents are increasingly being used for the treatment of T2D and obesity. Periconceptual exposure to these agents (sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RA) in an observational population-based cohort study using prescription data did not demonstrate an increased risk for major congenital anomalies, but the numbers were very limited and duration of exposure unclear. The most commonly used oral agents in pregnancy are glyburide (sulfonylurea) and metformin in GDM; these medications have not resulted in any increased risk in major congenital anomalies in large studies, but up to half of women with GDM taking either oral medicine will require insulin to achieve pregnancy targets.

GLYBURIDE IN GDM

Glyburide use has been associated with a higher rate of LGA compared to insulin. It increases placental GLUT1 expression in a dose-dependent fashion, potentially increasing glucose transport to the fetus in addition to having a possible influence on the fetal pancreas. If used at all during pregnancy, it should be limited to pregnant women with GDM who are not willing to use insulin. Meta-analyses comparing sulfonylureas to insulin in women with GDM have demonstrated increased rates of macrosomia and neonatal hypoglycemia. However, suboptimal dosing and timing of glyburide prior to meals and poor study designs may explain less favorable outcomes in prior studies.

Glyburide should be dosed preferably one hour before meals since the insulin stimulated by glyburide does not peak until 3–4 hours after meals. Because of its pharmacokinetic characteristics, glyburide should not be used before bedtime to target fasting hyperglycemia. About 20–35% of women with GDM will not achieve pregnancy targets with glyburide and thus its use in pregnancy is decreasing.

METFORMIN IN GDM AND IN ADDITON TO INSULIN IN T2D

Metformin use in GDM and T2D has been studied extensively in the last 20 years. Its lower risk of hypoglycemia, ease of use, and the challenges of treating a rapidly growing GDM population make it a desirable intervention for managing diabetes in pregnancy. However, it crosses the placenta even more so than glyburide with fetal concentrations often being greater than maternal concentrations. The MiG (Metformin in Gestation) RCT of 751 women with GDM, randomized to metformin or insulin at approximately 24–28 weeks, demonstrated no immediate adverse neonatal outcomes with decreased maternal weight gain and preeclampsia but higher TGs and preterm birth in the metformin group. In the metformin group, 46% of GDM women required supplemental insulin to meet glycemic pregnancy targets. The EMERGE RCT by Dunne et al. reported no difference in insulin initiation or fasting glucose >92 mg/dL at 32 or 38 weeks when metformin was started immediately upon diagnosis of GDM compared to placebo. The study also demonstrated overall lower birth weights (3393 ± 527 gm versus 3506 ± 510 gm; difference, −113 gm; *P* = .005) and a reduction of LGA (6.5% versus 14.9% placebo; *P* = .003) and macrosomia (7.6% versus 14.8% placebo; $P = .02$). Although not statistically significant, there was a clinically meaningful trend in infants <2500 gm (6.1% versus 3.4% placebo; $P = .12$), SGA (5.7% versus 2.7% placebo; $P = .13$), and shorter crown–heel length in metformin-exposed infants, suggesting a reduction in lean body mass. Whether the modest short-term benefits of metformin outweigh any potential increased risk of abnormal growth profiles or a reduction in infant lean body mass need to be investigated with long-term follow-up.

The MiTY and MOMPOD trials investigated the role of metformin starting in early gestation among women with T2D and early gestational age hyperglycemia who were receiving insulin therapy for diabetes management. The MiTY RCT, conducted in Canada and Australia, demonstrated no difference in the primary composite of fetal and neonatal outcomes but metformin-exposed pregnancies had significantly lower rates of gestational weight gain, overall total insulin dose, LGA, and macrosomia. However, the metformin-exposed group was associated with greater neonatal fat mass (6.2% versus 5.0%; $P = .017$), SGA (13% versus 7%; RR 1.96), and hyperbilirubinemia (23% versus 16%; RR 1.43). MOMPOD was a US multicenter randomized trial that included a more diverse population (29% Black and 52% Latinx) cohort, but the trial was discontinued at 75% accrual for futility in detecting a significant difference in the primary neonatal composite outcome (71% metformin-exposed versus 74% placebo; adjusted OR 0.86, 95% CI 0.63 to 1.19). Although the metformin-exposed group had lower odds of LGA (OR 0.63, 95% CI 0.46 to 0.86), the study was limited by self-reported adherence to the intervention and glycemic control parameters (HbA1C) are available in <40% of the cohort.

Metformin is crosses the placental readily and is concentrated in fetal and placental mitochondria 1000-fold. It has multiple intracellular effects, which can inhibit growth, suppress mitochondrial respiration, have epigenetic modifications on gene expression, mimic fetal nutrient restriction, and alter postnatal gluconeogenic responses. These findings raise concern about its potential effects on the developmental programming of metabolic disease in offspring. Childhood follow-up studies from trials using metformin among women with PCOS or GDM (MiG trial) demonstrate increased child weights and fat mass among offspring of mothers who were randomized to metformin. Follow up from the MiG trial did not show differences in glucose, lipids, insulin resistance, or liver function test measures in the offspring exposed to metformin compared to insulin. These growth findings in later childhood are consistent with animal studies, in which normally grown fetuses exposed to metformin exhibit postnatal overgrowth, particularly after exposed to a high-fat Western-style diet, underscoring the importance of long-term follow-up of these offspring and high-quality nutrition postnatally for long-term health prevention.

Although the Society of Maternal-Fetal Medicine supported metformin as an alternative to insulin in GDM, these recommendations did not include the more recent trials demonstrating the potential for SGA and did not address offspring long-term outcomes. Metformin should be used with caution in pregnancy. The ADA recommends insulin as the first-line agent in GDM and does not recommend metformin be added to insulin in T2D at this time. In a non-human primate model which have similar placentas as humans, metformin when given to pregnant monkeys resulted in similar fetal metformin levels as in human fetuses, reduced fetal skeletal muscle, and dysmorphology of the kidneys, potentially offering an explanation for the increase in SGA infants in some study (Bolte AJOG, 2024).

39. Discuss the use of glargine, detemir, and degludec during pregnancy.

All insulin formulations do not cross the placenta. “Expert Review” just featured in Obstetrics & Gynecology on Insulin Management in Pregnancy (Valent, 2024). Detemir was cleared by the FDA for use in pregnancy and may result in less nocturnal hypoglycemia than NPH, although the peaks of both detemir and NPH can be variable in pregnancy. For women with hepatic insulin resistance, NPH or detemir before bedtime may be needed to achieve sufficient fasting glucose control. Insulin glargine has been used extensively in pregnancy and has similar pregnancy outcomes. Glargine also has the advantage of being a flat-acting basal insulin with a minimal peak effect and can be used effectively with rapid-acting insulins. Degludec may also be used in pregnancy, but it is very long acting, resulting in a lag time when making insulin dose adjustments, which is often needed on a weekly or biweekly basis. Furthermore, due to the marked decrease in insulin requirements immediately postpartum, the very-long half-life of degludec may result in hypoglycemia after delivery.

40. What is the role of short-acting insulin analogs in pregnancy?

Lispro (Humalog) and Aspart (Novolog) are commonly used in pregnancy and have been shown to be safe and effective. Although immediate perinatal outcomes are similar between Regular insulin and Lispro, rapid-acting insulins improve glycemic control, allow flexibility in mealtimes, and can be used according to carb ratios and correction factors. They can achieve intensive control, decrease the risk of postprandial hypoglycemia, and lower total insulin requirements during pregnancy. Considering the pharmacokinetic challenges with Regular insulin peaking at 3–4 hours and lasting up to 8 hours, meal-timing is critical to ensure Regular insulin is administered at least 30–60 minutes prior to the first bite of food. The use of ultra-rapid-insulin analogs, such as Lyumjev and Fiasp, in pregnancy is increasing and they have also been shown not to cross the placenta.

41. Discuss fetal measures of well-being and surveillance required in pregnant persons with diabetes.

Pregnancies complicated by preexisting diabetes (T1D and T2D) have a fivefold higher rate of stillbirth that is unexplained in approximately 50% of cases. Although the causes of fetal death among women with diabetes are often not apparent, pregnant women with higher BMI, suboptimal glycemic control, and DKA during pregnancy clearly have increased risks of stillbirth. Fetal hyperglycemia and hyperinsulinemia result in excess fetal growth, increased fetal oxygen consumption, and relative tissue hypoxia. Fetal ischemia can be further exacerbated by decreased perfusion from placental insufficiency and preeclampsia at term. Fetal hypoxia and cardiac dysfunction, associated with cardiac enlargement and asymmetric septal hypertrophy, result from poor glycemic control and contribute to the long-term fetal programming of adult-onset disease.

All pregnancies complicated by diabetes are recommended to have an early ultrasound to confirm viability and dating of the pregnancy and a formal anatomy scan at 18–20 weeks to evaluate for fetal structural abnormalities. A fetal echocardiogram should be offered at 20–24 weeks for more detailed fetal cardiac evaluation if the HbA_{1C} was significantly elevated or cardiac anatomy was suboptimally viewed on a formal anatomy scan. Daily fetal movement monitoring should start at approximately 28 weeks and fetal surveillance should begin at approximately 32 weeks' gestation, possibly slightly earlier if glycemic control has been poor.

A fetal ultrasound for growth evaluation should be considered at 28–-32 weeks for women with preexisting diabetes. Those with newly diagnosed GDM and no prior level 2 anatomy scan should be referred to maternal-fetal medicine for a level 2 ultrasound assessment. Randomized controlled trials have demonstrated that if an ultrasound shows features of excessive fetal growth (especially a fetal abdominal circumference >90th% by 30–32 weeks) institution of tighter glycemic control among women with GDM was associated with lower rates of macrosomia and LGA infants. Rates of LGA were reduced with insulin treatment compared to lifestyle-only interventions, demonstrating a reduction in both mild maternal hyperglycemia and FFAs.

Frequency of growth ultrasounds can be increased with other obstetric indications. Having a growth ultrasound closer to anticipated delivery (approximately 36–37 weeks) can be considered for delivery planning. An estimated fetal weight ≥4500 gm is associated with increased risks for shoulder dystocia and birth injuries. These women should be counseled on the potential risks and the option of a cesarean birth discussed.

The optimal method or frequency of fetal surveillance to prevent adverse outcomes among women with preexisting diabetes and GDM is unknown. Women with preexisting diabetes, GDM requiring insulin, or those who have suboptimal glycemic control are recommended to initiate fetal nonstress testing (NST), modified biophysical profiles (amniotic fluid index plus fetal NST), or biophysical profile (ultrasound evaluation of fetal well-being) once or twice a week beginning at 32–34 weeks of gestation.

42. Discuss delivery timing among pregnant women with diabetes.

Many of the insulin resistance hormones begin to plateau at approximately 36 weeks, at which time insulin requirements often also plateau and may occasionally decrease by up to 15%. Fetal hyperinsulinemia may increase glucose uptake and clearance in fetal tissues, leading to an exaggerated or efficient glucose gradient from mother to fetus, potentially lowering maternal postprandial glucose, and resulting in what appears to be an improvement in glycemic control in the mother (fetal-placental steal syndrome). Additionally, rapid and marked decreases in insulin requirements may indicate worsening placental dysfunction with a decrease in placental hormones that promote insulin resistance; this should prompt an urgent fetal assessment and woman evaluation.

Delivery timing should be individualized for each woman, considering glycemic control, maternal comorbidities, and fetal well-being. Generally, women with GDM who are well controlled with lifestyle interventions alone may deliver between 39–41 weeks and those with GDM requiring medications with satisfactory glycemic control may deliver at 39–40 weeks. Delivery between 36–38 weeks should be considered for any type of diabetes with suboptimal glycemic control, especially when accompanied by Class 3 obesity, given the increased risk of stillbirth.

43. What are important aspects of postpartum management for women with preexisting or gestational diabetes?

New life adjustments, sleep deprivation, fatigue, erratic meal timing, metabolic changes, higher insulin sensitivity, and breastfeeding challenge the postpartum period. Issues that require attention to optimize postpartum health and recovery include maintaining appropriate glycemic control (70–180 mg/dL), sustaining high-quality nutrition practices, exercise and physical activity, breastfeeding, blood pressure and renal protection management, and contraception. The majority of postpartum women with preexisting diabetes have dramatic decreases in their insulin requirements immediately following delivery. Parents who are breastfeeding will likely require less than their prepregnancy doses.

Because postpartum women with GDM and preexisting diabetes are at risk for delayed onset of lactogenesis and lower breastmilk production, referral to a lactation specialist is valuable and encouraged. Both metformin and glyburide are considered safe to take while breastfeeding. A study reported that in 8 women in which breast milk was collected at 0, 12 and 24 h post-Semaglutide administration, Semaglutide was not detected in any of the collected human milk samples (Diab, 2024). Breastfeeding duration and intensity are associated with less atherogenic maternal lipid profiles and lower incidences of T2D and metabolic syndrome among women with a history of GDM and have also been shown to protect the offspring from childhood obesity.

Postpartum weight retention is unfortunately the norm and one of the strongest risk factors for progression to T2D or recurrence of GDM in a subsequent pregnancy. Weight loss after pregnancy may reverse or prevent progression to T2D. The postpartum period offers a unique opportunity to continue healthy habits learned during pregnancy; these can improve the long-term health of the postpartum person, child and entire family unit. However, continuity from prenatal to primary care among women with preexisting diabetes is often challenged by loss of follow-up and deterioration of glycemic control. Additionally, if effective contraception is not established, the woman is at risk for subsequent pregnancies with higher risks for adverse pregnancy outcomes.

Because decreased beta-cell function is already present in the prediabetic stage, women should be referred to a Diabetes Prevention Program, which focuses on achieving health goals through healthy nutrition and lifestyle behaviors under the direction of a health coach. Metformin should be considered for those who are not achieving their health goals. A subgroup analysis of the Diabetes Prevention Program (DPP) trial, examining women with high-risk factors for T2D, demonstrated participants with a history of GDM had a significantly higher risk of progression to T2D (11.4% per year) compared to women without a history of GDM (6.9% per year) over a 10-year follow-up period. Participants in the lifestyle intervention group (diet and exercise of 150 minutes per week and a 7% weight loss goal) showed a 35% reduction over the 10-year period. Similarly, participants randomized to metformin had a 40% risk reduction in the progression to T2D. If diet and exercise are unsuccessful or do not normalize glucose tolerance, metformin should be offered, especially in women with both impaired fasting glucose (IFG) and IGT.

The Nurses' Health Study II (n = 4275) investigated the individual and combined associations of optimizing modifiable risk factors (higher BMI, poor-quality eating patterns, lack of exercise, excess alcohol consumption, and current smoking) with the progression of T2D among participants with a history of GDM. For each additional modifiable factor that was optimized, there was an incrementally lower risk for progression to T2D, demonstrating that even small changes can lead to long-term rewards.

Women with a history of GDM should have cardiovascular and diabetes screening every 1–3 years following delivery in addition to discussing health goals with their primary care physician. Because parents highly influence their children's eating habits, sustaining healthy nutrition and lifestyle modifications learned during pregnancy is important to improve the overall health of the family unit. Children whose mothers emphasize health goals consume more healthy food and less unhealthy food.

44. Discuss the importance of glucose monitoring and testing during the postpartum period.

Home glucose monitoring should be continued in the postpartum period in women with preexisting diabetes because insulin requirements drop soon after delivery, increasing the risk of hypoglycemia. Although glycemic targets return to nonpregnant ranges in the postpartum period (70–180 mg/dL), glucose monitoring is important to keep glycemia within range to promote recovery and healing from cesarean incisions and perineal or vulvar lacerations. Immediately postpartum, women with GDM are generally followed with fasting and occasional post prandial glucose assessments to determine their metabolic status following delivery. If testing falls within relatively normal glycemic ranges, no further glycemic monitoring is recommended during the immediate postpartum period.

Women with a history of GDM have an increased risk for progression to T2D. A 75-gm 2-hr OGTT is recommended in the postpartum period in all GDM women to characterize glucose homeostasis following pregnancy and determine the potential risk for progression to T2D. Up to 70% of individuals with prediabetes on a 75 gm OGTT will progress to T2D by 5–10 years at a rate of approximately 5–10% per year. If only a FBG is measured, individuals with persistent IGT will be missed. HbA1c is not sensitive at 6 weeks postpartum since it is often confounded by iron deficiency anemia, postpartum blood loss, and postpartum fluid shifts; since HbA1c reflects glycemia over a 3-month period, this will include the latter 6 weeks of pregnancy.

The ADA and ACOG recommend retesting every 1–3 years using a FBG, HbA1c, or 75-gm 2-hr OGTT. Additionally, cardiovascular screening should be performed with similar frequency. The 75-gm 2-hr OGTT remains the most sensitive method for detecting any glucose intolerance but at a minimum, HbA1c levels should be checked. Many women with GDM covert to undiagnosed T2D before their next pregnancy, accompanied by an increased risk of major fetal anomalies if the A1C is >6.5%.

45. Discuss using the postpartum period as a window for preconception counseling and to encourage adequate contraception.

The postpartum period is preconception for subsequent pregnancies. Sustaining nutritional and lifestyle modifications implemented during pregnancy, continuing regular exercise, stabilizing mood and mindfulness, good sleep hygiene, and safe interventions for reducing pregnancy weight is essential to improve insulin sensitivity, long-term health, and prevent disease. Among women with Hispanic ethnicity and a history of GDM, weight gain postpartum is most strongly associated with declining beta-cell compensation. Frequent conversion to T2D after GDM is associated with greater interpregnancy weight retention compared to women who lose weight between pregnancies.

Reliable long-acting reversible contraception (LARC) is strongly encouraged for all women of reproductive potential following delivery. Contraception provides the opportunity to optimize health between pregnancies, prevent short-interval pregnancies, ensure appropriate prenatal supplements and nutrition are consumed, and reduce future adverse perinatal outcomes. Women with diabetes have been shown clearly to have better perinatal outcomes with preconception care and well-controlled glycemia. A preconception HbA1c target of <6.5% reduces the risk for congenital anomalies, miscarriage, and developmental fetal programming, but sadly, many women with GDM progress unknowingly to T2D before their next pregnancy, facing an increased risk of major malformations. Women with diabetes benefit from multidisciplinary care with their Primary Care, Endocrine, Obstetric, and other indicated subspeciality providers to individualize reliable contraception; optimize glycemic, cardiovascular, and renal profiles; identify and manage any micro- and macrovascular diseases; review medications; and improve preconception weight, nutrition, and lifestyle behaviors.

46. Which contraceptive agents can be used by women with diabetes or a history of gestational diabetes?

All contraceptive methods have good safety and overall efficacy among women with diabetes. Barrier and oral contraceptive methods are available but are challenged with inconsistent use that can lead to decreased efficacy. Hormonal contraception does not appear to advance microvascular disease or alter carbohydrate metabolism, but a woman with multiple cardiovascular risk factors should avoid combined oral contraceptive (COC) agents that contain estrogen. Women with poorly controlled hypertension or hypertriglyceridemia, or who are at risk for thromboembolic disease in addition to their diabetes are not good candidates for estrogen containing oral contraceptives. Triglycerides should be measured after the initiation of COC agents in women with diabetes or known hyperlipidemia given the higher incidence of hypertriglyceridemia and the associated risk of pancreatitis with oral estrogen use. Women who are heavier may have reduced efficacy when using some hormonal contraceptives including the transdermal patch and levonorgestrel emergency contraception. Drosperinone (Slynd) can be used in almost any woman with T1D, T2D, or GDM since it is an effective progesterone-only oral contraceptive with high efficacy, a favorable metabolic profile, and with no major contraindications. It should be considered for all women who do not desire pregnancy until further consideration for LARC can be done. Norethindrone alone (“Mini-pill”) is also safe, but less efficacious and must be taken at the same time every day.

LARC methods such as the intrauterine and implant devices are reliable, low-risk, and preferred methods for contraception to provide women control over their reproductive decisions. There is no increase in pelvic inflammatory disease with the use of intrauterine devices (IUD) in women with T1D or T2D after the postinsertion period and they provide contraception for 3 to 10 years.

The etonogestrel implant (Nexplanon®) does not worsen carbohydrate intolerance and is a good choice for individuals for up to 3 years. Depo-Provera (medroxyprogesterone acetate) is an option but is less metabolically favorable. Depo-Provera has been associated with an increased risk of T2D in lactating persons with a history of GDM secondary to the excess weight gain associated with its use. Bilateral tubal ligation is a permanent form of birth control that requires surgical intervention. It can be performed safely in women with diabetes with the best perioperative results when performed under good glycemic control. The significant benefits of nearly all contraceptives usually outweigh the risk of much higher pregnancy-associated hormones and the high maternal and fetal risks of unplanned or unwanted pregnancy.

47. How common is postpartum thyroiditis in women with type 1 diabetes? When does it appear?

Women with T1D have a three- to fourfold higher risk of developing postpartum thyroiditis than the general population (approximately 20%), particularly if they are thyroid peroxidase (TPO) antibody positive. The immunological rebound that follows the immune alterations of pregnancy can exacerbate an underlying autoimmune thyroiditis generally during the first year following delivery. The classic presentation for postpartum thyroiditis is a thyrotoxic phase that occurs 2–4 months postpartum, followed by a more common hypothyroid phase in the subsequent 4–8-month period, and then followed by a return to a euthyroid state by the end of the first year. However, it can also progress to permanent hypothyroidism and therefore annual testing is strongly recommended. Postpartum thyroiditis can also present with isolated mild thyrotoxicosis early or later hypothyroidism alone. Given the significance of this disorder, measurement of thyroid-stimulating hormone (TSH) is recommended in women with T1D who have positive TPO antibodies at 3 months and at 6 months after delivery or with any suggestive symptoms.

KEY POINTS

Diabetes in Pregnancy

- Although hyperglycemia is a major teratogen, the risk for congenital anomalies can be decreased to near baseline population risk with optimal glycemic control (HbA1c <6.5%) before pregnancy and during the first 10 weeks of gestation.
- Preconception counseling and effective contraception should be offered and optimally prescribed for all women whose diabetes and medical conditions have not yet been optimized or who are not desiring pregnancy due to the extremely high rate of unintended pregnancies.
- Diabetic ketoacidosis may occur at glucose levels less than 200 mg/dL in pregnancy (euglycemic DKA) and carries a high risk of intrauterine fetal demise for any pregnant woman with diabetes.
- CGM use in pregnant women with T1D has been shown to modestly improve glycemia, but to significantly decrease LGA and NICU admissions. It is now standard of care for use in pregnant women with T1D alongside self-monitoring blood glucose.
- Pregnancy does not usually accelerate the progression of diabetic nephropathy unless it is already severe, but proteinuria, proliferative retinopathy, and autonomic neuropathy may worsen.

KEY POINTS—cont'd

- Insulin requirements often decrease in the first trimester placing the pregnant woman with T1D at high risk of severe hypoglycemia; insulin requirements may double to quadruple in the late second and third trimesters due to the insulin resistance of pregnancy.
- All insulins can be used in pregnancy; it has not been established whether pump therapy improves pregnancy outcomes in T1D compared to intensive insulin regimens using MDI. HCL pump trials are ongoing.
- Pregnant individuals who develop GDM have a 30–74% risk of developing T2D within 5 to 10 years. Preventative measures for the development of T2D should be instituted postpartum and individuals should be screened every 1–3 years for the progression to T2D, which often occurs before the next pregnancy.
- Use of oral agents for GDM and of metformin in combination with insulin in T2D is controversial since metformin and glyburide both cross the placenta. Both may have long-term developmental programming effects with some data suggestive of increased childhood overweight in those offspring exposed *in utero* to metformin.
- Both the 1-step and 2-step approaches to diagnosing GDM are acceptable. Although there is a lack of consensus for early screening for GDM, the ADA suggests that at least individuals who have not been screened for T2D prior to pregnancy should be universally screened for undiagnosed diabetes at <15 weeks of gestation. Standard diagnostic criteria for diagnosing T2D outside of pregnancy may be used in pregnancy.
- Maternal, placental and fetal carbohydrate requirements in the third trimester of pregnancy are estimated to be at least 175 gms. A healthy eating pattern that is low in saturated fats and higher in complex carbohydrates with avoidance of simple carbohydrates is also a safe option. The ADA 2024 and USDA endorse a balance of macronutrients including nutrient-dense fruits, vegetables, legumes, whole grains, and healthy fats with omega-3 fatty acids that include nuts and seeds and fish in the eating patterns.
- The intrauterine environment characterized by glucose and lipid excess and insulin resistance in individuals with T1D, T2D, and GDM appears to influence long-term fetal programming effects that contribute to offspring childhood obesity and cardiometabolic disease risk.

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CHAPTER 9

Diabetes Management in Cancer Patients

Elizabeth Tupta

1. Is diabetes associated with cancer risk?

Yes. People with diabetes have a 20–25% increased risk for developing cancer compared to those without diabetes. Most studies have evaluated cancer risk and type 2 diabetes (T2DM) and found T2DM to be associated with a 2-fold higher risk for liver, pancreatic, and endometrial cancers and a 1.5-fold increased risk for colon, rectal, ovarian, and bladder cancers. The relationship between cancer risk and type 1 diabetes (T1DM) has been less well studied, but it also appears to be associated with an increased malignancy risk, especially for liver, pancreatic, and endometrial cancers, and also for thyroid, stomach, kidney, and lung cancers.

Whether the relationship between diabetes and cancer is causal or correlational is unclear. Possible direct mechanisms for increased cancer risk include hyperglycemia, hyperinsulinemia, high levels of IGF-1, increased inflammatory cytokines, and alterations of insulin signaling pathways. Indirect links include common underlying risk factors such as age, obesity, alcohol, physical activity, and smoking. More rigorous studies are needed to determine whether there is a direct causal relationship between diabetes and cancer.

2. Do people with diabetes and cancer have a worse prognosis?

Studies support that adults with diabetes also have a higher risk of cancer mortality compared with individuals without diabetes (hazard ratio = 1.25). The strongest mortality risk has been associated with liver, colorectal, ovarian, lung, bladder, and breast cancers. This risk was significantly reduced after adjusting for fasting glucose and hemoglobin A1c levels, supporting that poor glycemic control negatively affects cancer outcomes.

3. What are factors that may contribute to an increased cancer mortality risk in diabetes patients?

1. Hyperglycemia:
    - Promotes tumor cell metabolism and growth through increased glucose uptake.
    - Stimulates IGF-1 pathways promoting angiogenesis and metastases.
    - Increases levels of reactive oxygen species (ROS), which may promote DNA mutations and promote tumor-cell progression.
2. Hyperinsulinemia:
    - Stimulates insulin and IGF-1 receptors, which are expressed by cancer cells and are responsible for tumor growth, invasion, and metastases.
    - Increases free estrogen and testosterone levels in women and men through decreased hepatic synthesis of sex-hormone-binding globulin (SHBG) and increased androgen production by the ovaries, increasing the risk of breast and endometrial cancers.
3. Inflammatory cytokines:
    - Insulin resistance and associated obesity cause an increase in free fatty acids and proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, all of which may play a role in malignancy and cancer progression.
4. Compromised immune system:
    - Impaired innate immunity may decrease efficacy of cancer therapies.
5. Comorbid conditions:
    - Individuals with diabetes are at higher risk of having other underlying comorbidities, such as cardiovascular disease, kidney disease, and peripheral neuropathy, which may limit the ability to provide aggressive therapy and increase the risk for dose-limiting toxicities.

4. Why is glycemic control important in the cancer population?

Hyperglycemia has been associated with an increased risk for infection, hospitalization with increased length of stay, cancer progression, and overall mortality. Hyperglycemia may also contribute to malnutrition and weight loss and exacerbate fatigue as well as diabetic complications such as neuropathy. Therefore effectively treating hyperglycemia may improve cancer outcomes while enhancing quality of life.

5. What are appropriate glycemic targets for cancer patients?

Currently there are no guidelines that establish glycemic targets for patients with cancer and diabetes. Clarification of treatment goals requires a collaborative discussion between patients, families, and providers. When determining A1c targets, providers should consider similar factors as the general diabetes population, including hypoglycemia risk, life expectancy, financial limitations, available support, and patient preferences. Additional unique considerations include cancer therapy side effects that increase the risk for hypoglycemia, such as nausea, vomiting, and malnutrition.

It is important to educate patients and families early regarding the potential shift in glycemic targets based on the course of the cancer trajectory. In general, the goal A1C is 7% to 8%, with a higher target closer to 8.5% in those with increased frailty and hypoglycemia risk. For patients who are terminally ill, glycemic targets should shift from focusing on the A1C to the prevention of hypoglycemia and symptomatic hyperglycemia. For patients with a prognosis of months to years, the suggested glycemic targets are 100–200 mg/dL and for a prognosis of days to weeks 200–300 mg/dL.

7. List available antidiabetic therapies for oncology patients and special considerations when selecting an optimal diabetes regimen.

When selecting appropriate diabetes therapies, the American Diabetes Association (ADA) guidelines for pharmacologic management should be followed. Table 9.1 lists available therapies and unique factors to consider within the cancer population.

8. Explain how metformin may improve cancer outcomes.

Metformin is considered the first-line antidiabetic drug of choice for individuals with cancer because of its efficacy, safety, and antitumor effects. There are multiple proposed mechanisms that may contribute to metformin's anticancer effects: (1) decreased protein synthesis and cell growth through adenosine monophosphate kinase (AMPK) activation and mechanistic target of rapamycin (mTOR) inhibition; (2) the induction of tumor-cell apoptosis; (3) decreased circulating insulin levels; (4) immune system activation; and (5) destruction of cancer stem cells. Research supports that metformin may work adjunctively with chemotherapy to reduce tumor size and metastasis risk and is associated with a lower risk of relapse and mortality. Metformin has also been shown to enhance the effect of radiotherapy by increasing ROS, leading to increased DNA damage.

9. What cancer therapies are associated with an increased risk for hyperglycemia in cancer patients with or without underlying diabetes?

Because many cancer therapies affect pathways that regulate glucose and insulin metabolism, individuals receiving cancer therapies, with or without underlying diabetes, are at high risk for developing hyperglycemia during cancer treatment. Hyperglycemia is one of the most common toxicities for phosphoinositide 3-kinase (PI3K)/AKt pathway inhibitors used for the treatment of breast cancer, with up to 65% of patients who receive alpelisib experiencing high blood sugars. mTOR inhibitors, which work within the PI3K signaling pathway, are also used in breast cancer therapy and similarly cause a high incidence of hyperglycemia, ranging from 13% to 50%. Tyrosine kinase inhibitors (TKIs) are a broad class of targeted therapies that include epidermal growth factor receptor (EGFR) (erlotinib) and BCR-ABL1 (imatinib) inhibitors. TKIs are used for the treatment of certain lung cancers and chronic myelogenous leukemia (CML) and have been linked to both hypoglycemia and hyperglycemia. Immune checkpoint inhibitors (ICIs), which are used in numerous malignancies, such as metastatic melanoma, lymphoma, and lung cancer, have caused a novel type of autoimmune diabetes referred to as *checkpoint inhibitor autoimmune diabetes* (CIADM). Additionally, treatment with glucocorticoids (GCs) is associated with a high incidence of hyperglycemia, ranging from 30% to 50% in hospitalized patients without a prior history of diabetes. Please refer to Table 9.2 for a complete list of cancer therapies associated with hyperglycemia, along with recommended monitoring and treatments.

TABLE 9.1 Antidiabetic Therapy and Special Considerations for the Oncology Population

DRUG	SPECIAL CONSIDERATIONS
Biguanides	• Considered drug of choice for patients with cancer and diabetes • Antitumor effects • Avoid if nausea, vomiting, or malnutrition • Available in liquid form if difficulty swallowing • Consider alternative if frequent need for CT imaging with contrast and eGFR <60 • Contraindicated if eGFR <30 or active liver disease
Sulfonylureas	• Avoid if high hypoglycemia risk • Avoid if irregular eating patterns • Avoid if decreased PO intake, nausea, or vomiting • Alternative to insulin for treatment of steroid-induced hyperglycemia
Meglitinides	• Avoid if high hypoglycemia risk • Avoid if decreased PO intake, nausea, or vomiting • May consider "as needed" if irregular eating patterns
Thiazolidinediones	• Avoid if history of bladder cancer • Contraindicated if active bladder cancer or heart failure
DPP-4 inhibitors	• Avoid if pancreatitis risk • Avoid saxaglitptin and alogliptin if heart failure • Renal dosing for sitagliptin, saxagliptin, alogliptin
GLP-1 agonists	• Avoid if pancreatitis risk • Avoid if weight loss, decreased PO intake, nausea, or vomiting • Contraindicated if personal or FH of medullary thyroid cancer
SGLT-2 inhibitors	• Avoid if weight loss, decreased PO intake, nausea, or vomiting • Avoid use for glycemic control if eGFR <30 • Consider DKA risk • Canagliflozin associated with increase renal cell carcinoma risk
Insulin	• Drug of choice if severe hyperglycemia, symptomatic hyperglycemia or CIADM • Best option if anorexia, weight loss, or muscle wasting • Choose rapid-acting insulin if erratic eating patterns • Consider NPH with steroid-induced hyperglycemia

10. Explain how ICIs work and how these therapies cause autoimmune diabetes.

Programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4) are regulatory proteins that promote self-tolerance by preventing T-cell activation. Tumor cells evade the immune system by expressing ligands that activate these inhibitory pathways, allowing the tumor cells to survive. ICIs are monoclonal antibodies that target PD-1, its ligand (programmed cell death protein 1 ligand [PD-L1]), or CTLA-4 to promote T-cell activation and tumor cell death. PD-1 and PDL-1 inhibitors have been associated with CIADM.

We know that T1DM is caused by autoimmune destruction of insulin-producing beta cells. There is also evidence to support the involvement of the PD-1 pathway in the development and progression of autoimmune diabetes. PDL-1 is expressed on inflamed pancreatic islet cells, allowing for the inhibition of autoreactive T cells and preventing the destruction of beta cells. Studies investigating the development of autoimmune diabetes with the nonobese diabetic mouse model have shown that PD-1 blockade precipitates the rapid development of autoimmune diabetes. Furthermore, there is evidence that humans with T1DM have a significantly lower expression of PD-1 in CD4+ T cells compared with the general healthy population. Therefore it is proposed that treatment with a PD-1/PDL-1 inhibitor blocks this inhibition and allows for the activation of autoreactive T cells, leading to the destruction of beta cells.

11. Have CTLA-4 inhibitors been associated with CIADM?

There have been very few case reports of CIADM associated with CTLA-4 monotherapy, with most cases also receiving previous PD-1 therapy. In animal models, inflamed beta cells had increased expression of PD-L1 but not ligands of CTLA-4 during the development of

TABLE 9.2 Cancer Therapies Associated With Hyperglycemia

DRUG	MECHANISM OF HYPERGLYCEMIA	ONSET	MONITORING	INTERVENTIONS
ICIs (Programmed cell death 1 [PD-1]/ Programmed cell death 1 ligand [PD-L] inhibitors [pembrolizumab] as monotherapy or combined with cytotoxic T lymphocyte associated antigen-4 [CTLA-4] inhibitors [ipilimumab])	PD-1 blockade allows for beta cell destruction by autoreactive T-cells	1–52 weeks	Blood glucose (BG) at baseline and prior to each infusion x 12 weeks, then every 3–6 weeks	• If e/o DKA, treat per institution guidelines • Initiate insulin therapy if FBG >160 mg/dL and concern for T1DM **If BG >250 mg/dL** • Hold therapy and evaluate for DKA • Evaluate for T1DM • Initiate insulin therapy
TKIs-EGFR/BCR-ABL inhibitors (nilotinib, sunitinib)	• Unknown • Some TKIs associated with hypoglycemia (imatinib and dasatinib)	1–3 weeks	• Fasting BG (FBG) baseline, and day 1, 8, and 15 of each cycle • Start home monitoring 2x daily if FBG >160 or any random BG >200	• Start metformin 500 mg BID if 2 BG values >160 mg/dL in 1 week • Hold therapy if FBG >500 mg/dL, restart when FBG <250 mg/dL and consider dose reduction
PI3K-AKT-mTOR inhibitors (alpelisib, idelalisib, everoliums)	• ↑ insulin resistance, ↓ insulin secretion, ↓ glycogen synthesis ↓ glucose utilization	1–2 weeks	• FBG and A1C at baseline and every 3 months **No preexisting DM:** • FBG weekly x 2 weeks, then every 4 weeks • Start home BG monitoring once FBG > 160 or any random BG >200 **Preexisting DM:** • Increase frequency of home monitoring to 3x daily for at least the 1st 4 weeks	
AntiCD30 drug conjugate (Brentuximab)	• Unknown Proposed mechanisms: • cytokine release syndrome • Type B insulin resistance syndrome	1–4 weeks	• Monitor BG levels prior to each treatment • Home monitoring for 1–2 weeks post infusion • Ensure home monitoring with existing DM	• Insulin therapy initially, usually requiring intravenous insulin therapy • Insulin therapy often not required after initial hyperglycemic episode • Dose reduction with subsequent cycles
Platinum Analogs (Cisplatin)	• Unknown	1–2 weeks	• Monitor BG weekly after infusion	• Initiate antidiabetic therapy if BG values >180 mg/dL x2 or HgbA1C ≥7% • Treat DKA/HHS per institution guidelines

Continued

TABLE 9.2 Cancer Therapies Associated With Hyperglycemia—cont'd

DRUG	MECHANISM OF HYPERGLYCEMIA	ONSET	MONITORING	INTERVENTIONS
Glucocorticoids	• ↑ insulin resistance • ↓ insulin release	• Usually within 48 hours • May occur later with longer steroid duration/ exposure	• Monitor BG before meals and bedtime (ACHS) x48 hours if no preexisting DM • Increase BG monitoring to ACHS if preexisting DM	• Initiate NPH at the same time as steroid dose or basal (30%)/bolus (70%) therapy if BG values >180 mg/dL x2 OR if preexisting DM with A1C > 7.5% or requiring ≥20 units of correction/24 hours • May consider SU in place of insulin
Calcineurin inhibitors	• ↑ insulin resistance • ↑beta cell apoptosis	• Days to weeks • Risk decreases with dose decrease	• Routine lab monitoring per transplant protocol • Initiate home BG monitoring with serum BG >180 mg/dL	• Initiate antidiabetic therapy if BG values >180 mg/dL x2 or HgbA1C ≥7%
Hormone-based therapies	• ↓ Insulin secretion • ↑ Insulin resistance	• Risk increases >2 yrs on SERM and >6 mo on ADT	• Initiate home BG monitoring if serum BG >180 mg/dL	• Initiate antidiabetic therapy if BG values >180 mg/dL x2 or HgbA1C ≥7%

autoimmune diabetes. It is proposed that CTLA-4 affects naïve T cells while the PD-1 pathway seems to play a role in regulating autoreactive T cells throughout the life span.

12. What is the incidence of CIADM?

CIADM is very rare, with incidence rates of between 0.1% and 1% reported.

13. How do patients with CIADM typically present?

Affected individuals often present with an acute onset of hyperglycemia with diabetic ketoacidosis (DKA). The A1c level is usually only moderately elevated (median 7.6%), with a typically low or undetectable C-peptide, supporting a short duration of hyperglycemia and rapid beta-cell destruction. Approximately 50% of people with CIADM have diabetes-associated antibodies, and this has been associated with a quicker onset of diabetes and higher incidence of DKA at presentation. All patients reported to have positive antibodies have had positive antiglutamine acid decarboxylase (GAD) antibodies.

14. What are risk factors for developing CIADM?

Underlying autoimmune disease and other autoimmune adverse effects secondary to ICIs are associated with a higher risk of developing CIADM. People who develop CIADM often experience other autoimmune adverse effects, such as thyroiditis, pancreatitis, and colitis, either before, during, or after developing autoimmune diabetes. Human leukocyte antigen (HLA) haplotypes have been associated with T1DM, specifically the (DR3-DQB1*02:01 and/or DR4-DQB1*03:02). The majority of CIADM cases reported have had at least one high-risk DR or DQ allele associated with T1DM.

15. How is CIADM different from T1DM?

In contrast to the younger age of onset usually associated with T1DM, the median age of onset for CIADM is 63 years. While people with T1DM often go through a “honeymoon period,” individuals with CIADM have a rapid decline in C-peptide levels with no apparent honeymoon phase. Unlike T1DM, CIADM has a lower association with insulin autoantibodies. When comparing CGM data from people with CIADM to those with T1DM, there were no apparent differences in glycemic variability.

16. How do you monitor for CIADM?

Please refer to Table 9.2 for specific monitoring guidelines. Providers should educate people on the signs and symptoms of hyperglycemia and DKA prior to the initiation of ICIs and consider providing those with a history of autoimmune disease and/or autoimmune adverse ICI effects with a glucometer for closer monitoring. Currently, it is not recommended that HLA or autoantibody screening be performed.

17. What is the recommended treatment for CIADM?

Treatment includes evaluation and treatment for DKA and initiation of insulin therapy. Treatment with corticosteroids is not recommended because there is no evidence of clinical efficacy, and these agents will contribute to worsening glycemic control. Please refer to Table 9.2.

18. Explain how PI3K-AKT-mTOR inhibitors cause hyperglycemia.

Hyperglycemia is the most common side effect of these therapies and is considered an on-target effect. The PI3K-AKT pathway regulates glucose metabolism through insulin signaling, whereas mTOR complex 1 regulates beta-cell function. Inhibiting this pathway reduces glucose uptake in adipose tissue and skeletal muscle, reduces glycogenesis, promotes glycogenolysis, and may impair insulin secretion.

19. What is the recommended diabetes therapy for hyperglycemia secondary to PI3K-AKT-mTOR inhibitors?

Please refer to Fig. 9.1.

20. Describe how certain diabetes therapies may affect the efficacy of PI3K pathway inhibitors.

Insulin stimulates the PI3K pathway. Hyperglycemia caused by PI3K inhibitor therapy results in compensatory hyperinsulinemia that reactivates the PI3K pathway and may decrease the efficacy

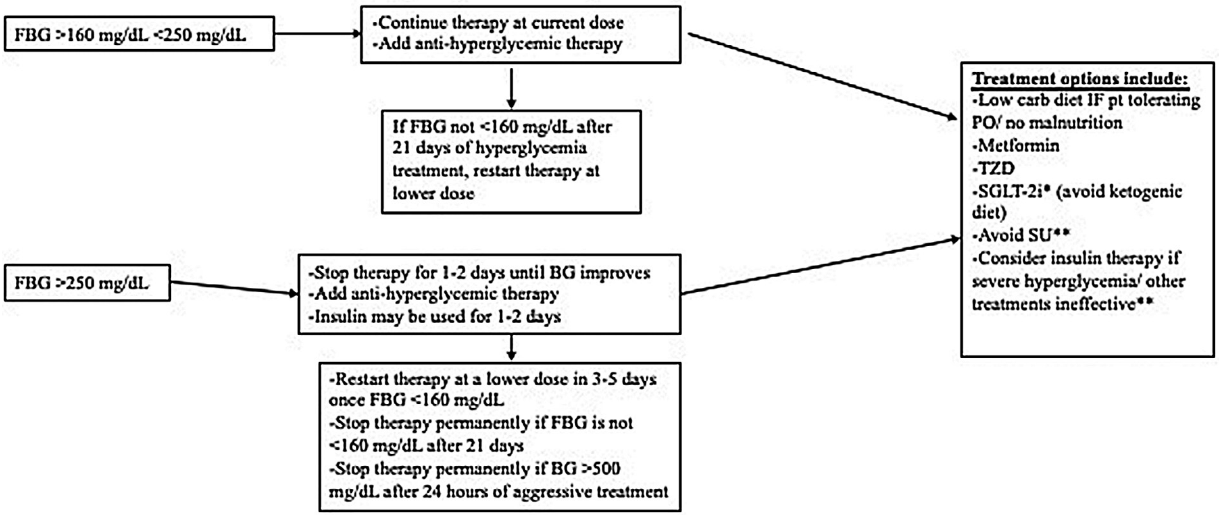
FBG >160 mg/dL <250 mg/dL
-Continue therapy at current dose
-Add anti-hyperglycemic therapy
If FBG not <160 mg/dL after 21 days of hyperglycemia treatment, restart therapy at lower dose
FBG >250 mg/dL
-Stop therapy for 1-2 days until BG improves
-Add anti-hyperglycemic therapy
-Insulin may be used for 1-2 days
-Restart therapy at a lower dose in 3-5 days once FBG <160 mg/dL
-Stop therapy permanently if FBG is not <160 mg/dL after 21 days
-Stop therapy permanently if BG >500 mg/dL after 24 hours of aggressive treatment
Treatment options include:
-Low carb diet IF pt tolerating PO/ no malnutrition
-Metformin
-TZD
-SGLT-2i* (avoid ketogenic diet)
-Avoid SU**
-Consider insulin therapy if severe hyperglycemia/ other treatments ineffective**

Fig. 9.1 Treatment of hyperglycemia secondary to PI3K-AKT-mTOR inhibitor therapy.
*May increase PI3K inhibitor effectiveness.
**May decrease PI3K inhibitor effectiveness.

of treatment. There is some evidence that sodium glucose co-transporter 2 (SGLT2) inhibitors effectively reduce BG and subsequent hyperinsulinemia after treatment with PI3K pathway inhibitors and reduce tumor signaling. Therefore SGLT2 inhibitors may increase PI3K inhibitor treatment effectiveness. Ketogenetic diets have also been demonstrated to reduce tumor signaling secondary to hyperinsulinemia; however, carbohydrate restriction should not be enforced for patients who struggle with nausea, vomiting, weight loss, and/or malnutrition. Furthermore, ketogenic diets should be avoided with SGLT2 inhibitor therapy because of the increased risk for DKA associated with this medication class. Insulin and sulfonylureas should be avoided, since these have been associated with increased tumor signaling and may reduce the antitumor efficacy of PI3K therapy. Insulin therapy may still need to be considered when there is difficulty achieving glycemic control or with high grade hyperglycemia.

21. Describe the pattern of GC-induced hyperglycemia.

GCs tend to have less effect on fasting BG but often cause large postprandial BG excursions and peak BG levels after lunch and dinner. Therefore it is important to monitor afternoon and evening BG when people are taking high doses of GCs. The duration of hyperglycemia depends on the type and dosing of the steroid. For example, BG tends to be elevated for 12 hours after AM prednisone dosing, followed by an overnight BG drop; in contrast, daily dexamethasone may cause hyperglycemia for up to 72 hours after each dose, with a steady state of hyperglycemia unrelated to meals for the first 24 hours.

22. How do you monitor for GC-induced hyperglycemia?

For prednisone equivalent >7.5 mg daily:

- No preexisting diabetes: Monitor BG levels three to four times daily before meals for 48 hours and stop if BG values are consistently under <180 mg/dL.
- Preexisting diabetes: Increase the frequency of home glucose monitoring to include before meals and at bedtime.

23. When should you initiate additional antidiabetic therapies for GC-induced hyperglycemia?

- No preexisting diabetes: BG >180 mg/dL x 2
- Preexisting diabetes: Currently on insulin therapy *OR* A1C >7.5% on non-insulin meds *OR* receiving >20 units of correction insulin/24 hours

24. Discuss treatment strategies for GC-induced hyperglycemia.

It is recommended to administer weight-based intermediate-acting human insulin (neutral protamine Hagedorn [NPH]) once daily at the same time as the steroid (see Chapter 7 for dosing recommendations). This method is preferred for shorter-acting steroids (prednisone, prednisolone), since the onset, peak, and duration of NPH matches the glycemic profile of GC-induced hyperglycemia. NPH administered once daily is also more convenient than multiple daily injections. For longer-acting steroids (dexamethasone) or dosing multiple times per day, treatment with basal-bolus therapy is another option, with 25–30% of the total daily dose distributed as basal insulin and 70–75% as bolus insulin. For people who wish to avoid injections, a sulfonylurea such as glipizide may be needed to control postprandial BG excursions.

25. Discuss options to treat hyperglycemia related to dexamethasone therapy.

Dexamethasone is a common GC used within the cancer population. This is often given with chemotherapy to prevent nausea and vomiting. Given its high potency and longer duration of action, this makes it especially challenging to safely and effectively manage hyperglycemia related to this therapy. For dexamethasone doses 6 mg or greater, it is recommended to administer NPH 0.3–0.4 units/kg at the same time as the steroid. This can be added to the cancer treatment plan in coordination with oncology to ensure insulin is timed with each dose of steroid, or the patient can self-administer at the same time as dexamethasone each cycle. Given the longer duration of hyperglycemia associated with dexamethasone, an additional dose of NPH at bedtime may be necessary to treat fasting hyperglycemia. Basal-bolus therapy may also be considered; however, often patients will require NPH in addition to effectively manage hyperglycemia. If a person is already on insulin therapy, the individual may require an increase in insulin dosing for up to 72 hours after dexamethasone is administered. It is recommended to closely monitor BG trends with a continuous glucose monitor (CGM) to assist the provider in making appropriate adjustments after each treatment cycle.

TABLE 9.3 End-of-Life Diabetes Management

	TYPE 2 DM	TYPE 1 DM
BG monitoring frequency*	• No insulin: stop • On insulin: once daily • Continuous glucose monitor: continue per individual/ family preference	• Once daily • Continuous glucose monitor: continue per individual/ family preference
BG targets*	• Avoid symptomatic hyperglycemia and hypoglycemia • Consider target of 200–300 mg/dL**	• Avoid ketoacidosis/ symptomatic hyperglycemia and hypoglycemia • Consider target of 200–300 mg/dL**
Orals/GLP-1 agonists	Stop	• N/A
Insulin therapy***	• Stop prandial insulin • Consider stopping basal based on glycemic control and current dose • Continue insulin pump if individual/ family preference and pump competency • Reduce insulin dose by 25%	• Stop prandial insulin • Continue basal insulin therapy • Continue insulin pump if individual/ family preference and pump competency • Reduce insulin dose by 25%

*Frequency of BG monitoring and BG targets should be determined in coordination with patient and family.
**Recommended BG targets vary based on guidelines.
***Insulin regimen should be determined in coordination with patient and family preference. Recommend discussing goals of care with patient and family at the time of diagnosis.

26. How do you manage hyperglycemia in terminal illness?

There are limited guidelines available that provide recommendations regarding diabetes management during the end of life. Evidence to support these recommendations is mostly limited to expert opinion. The goal of diabetes management is to reduce symptomatic hyperglycemia while avoiding hypoglycemia. Diabetes regimens should be simplified and fingersticks reduced. Insulin and/or oral agents should be adjusted based on phase of terminal illness, oral intake, organ dysfunction, and risk of hypoglycemia, while also considering patient and family preferences. See Table 9.3 for a management algorithm.

KEY POINTS

- Diabetes is correlated with an increased cancer risk and increased cancer mortality risk.
- Uncontrolled hyperglycemia is associated with increased infection risk, higher symptom burden, malnutrition, and worse cancer outcomes.
- There are numerous cancer therapies that cause hyperglycemia, including ICIs, TKIs, mTOR inhibitors, PI3K pathway inhibitors, and steroids.
- CIADM is distinct from T1DM with rapid C-peptide decline and low association with diabetic-associated antibodies.
- End-of-life care should focus on reducing hypoglycemia and symptoms of hyperglycemia.

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CHAPTER 10

Hypoglycemic Disorders

Helen M. Lawler

1. What is the definition of hypoglycemia in people without diabetes?

In an individual without diabetes, hypoglycemia is defined by the presence of Whipple's triad:

1. Hypoglycemic symptoms
2. Plasma glucose (PG) level <55 mg/dL (<3 mmol/L) while symptoms are occurring
3. Resolution of hypoglycemic symptoms with correction of the low PG level

2. What are the clinical symptoms of hypoglycemia?

The symptoms of hypoglycemia can be divided into *neurogenic symptoms* and *neuroglycopenic symptoms.* Neurogenic symptoms are catecholamine mediated (palpitations, tremulousness, anxiety) and cholinergic mediated (hunger, diaphoresis, paresthesias). Neuroglycopenic symptoms occur due to inadequate glucose delivery to the brain and include mental fogginess, confusion, irritability, behavioral changes, seizures, loss of consciousness, and coma.

3. What is the importance of the timing of these symptoms in relation to food intake?

Fasting hypoglycemia refers to low PG levels that occur more than 4 hours after the last meal, especially after missed meals or an overnight fast. *Postprandial hypoglycemia* (formerly known as *reactive hypoglycemia*) occurs within 4 hours after food intake. Postprandial hypoglycemia is typically seen with post bariatric hypoglycemia (PBH) and the noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). Patients with insulinomas typically have fasting hypoglycemia, but postprandial hypoglycemia can also occur. Because many conditions can cause fasting and/or postprandial hypoglycemia, the timing of the hypoglycemia in relation to meals is not always a reliable indicator of the etiology.

4. What are the causes of hypoglycemia in adults?

The causes of hypoglycemia are usually divided into those that are insulin mediated (hyperinsulinemic hypoglycemia) and those that are non-insulin mediated.

Hyperinsulinemic Hypoglycemia	*Non–Insulin-Mediated Hypoglycemia*
Insulinoma	Critical illness (sepsis) or organ failure (hepatic, renal, or heart failure)
Postbariatric hypoglycemia (PBH)	Starvation
Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)	Alcohol
Exogenous insulin therapy for diabetes	Glycogen storage diseases or other hepatic enzyme defects
Insulin secretagogue therapy for diabetes (sulfonylureas, meglitinides)	Adrenal insufficiency
Factitious hypoglycemia (surreptitious insulin or insulin secretagogue use)	Non–islet cell tumors (insulin-like growth factor [IGF] mediated)
Insulin autoimmune syndrome (antibody to insulin or insulin receptor)	Consumption of unripe ackee fruit ("Jamaican vomiting sickness")
Nondiabetes drugs	Nondiabetes drugs

5. What is idiopathic postprandial syndrome?

Idiopathic postprandial syndrome refers to symptoms suggestive of hypoglycemia that occur after eating but without biochemical evidence of hypoglycemia. Once other etiologies for hypoglycemia-like symptoms (i.e., anxiety, hyperthyroidism, menopause, migraines, and pheochromocytoma) have been excluded, it is then more appropriate to identify those symptoms without biochemical hypoglycemia (and, thus, absent Whipple's triad) as idiopathic postprandial syndrome. Frequently, underlying anxiety, neuropsychiatric disease, or situational stress reactions are the real culprits of idiopathic postprandial syndrome, which the patient characterizes or self-diagnoses as hypoglycemia.

6. What are the artifactual causes of hypoglycemia?

Pseudohypoglycemia occurs in some chronic leukemias when the leukocyte counts are markedly elevated. This artifactual hypoglycemia results from utilization of glucose by leukocytes after the blood sample has been drawn. Pseudohypoglycemia may also occur with hemolytic anemia or polycythemia vera through similar mechanisms. In addition, a discordance between capillary and venous glucose levels can cause pseudohypoglycemia. This has been reported in patients with Raynaud's phenomenon, peripheral vascular disease, and shock resulting from low capillary blood flow. Artifactual hypoglycemia may also be seen with improper sample collection or storage, errors in analytic methodology, or confusion between whole blood and plasma glucose values. Plasma glucose is about 15% higher than the corresponding whole BG values.

7. When hypoglycemia occurs, what counterregulatory events occur to preserve glucose for brain metabolism?

A normal initial physiologic response to declining PG levels is suppression of insulin secretion and stimulation of glucagon and epinephrine secretion. Glucagon and epinephrine are the dominant counterregulatory hormones. Their metabolic effects are immediate: stimulation of hepatic glycogenolysis and later gluconeogenesis, resulting in increased hepatic glucose production to restore PG levels to the physiologic range. Glucagon is the more important counterregulatory hormone present during acute hypoglycemia, since epinephrine does not appear to be essential if glucagon is present. If glucagon secretion is decreased or absent, epinephrine serves as the principal counterregulatory hormone. Other hormones that respond to hypoglycemic stress are cortisol and growth hormone, but their effects are delayed.

8. What is hyperinsulinemic hypoglycemia, and which conditions cause islet beta cell hyperfunction?

Hyperinsulinemic hypoglycemia refers to hypoglycemia (PG <55 mg/dL [<3 mmol/L]) associated with a serum insulin level ≥3 μU/mL, C-peptide ≥0.2 nmol/L, proinsulin ≥5 pmol/L, and beta-hydroxybutyrate ≤2.7 mmol/L. If hyperinsulinemic hypoglycemia is present, a glucose rise of >25 mg/dL (1.4 mmol/L) is also anticipated in response to administration of intravenous glucagon. This is because elevated insulin levels inhibit hepatic glycogenolysis and preserve hepatic glycogen stores. Glucagon administration causes the release of glucose from the preserved hepatic glycogen stores. Hyperinsulinemic hypoglycemia suggests the presence of islet beta cell hyperfunction (insulinoma, NIPHS, or PBH), therapeutic or surreptitious use of insulin or oral hypoglycemic agents, or insulin autoimmune syndrome.

9. Which laboratory tests are useful in evaluating Whipple's triad?

Once Whipple's triad is confirmed, a complete blood count, comprehensive metabolic panel, 8 AM serum cortisol level, and serum insulin antibody levels should be collected at the clinic visit. Of note, insulin antibody levels may be positive in patients who have taken insulin in the past. To determine if insulin-mediated hypoglycemia or non–insulin-mediated hypoglycemia is present, it is important to obtain fasting values for serum insulin, proinsulin, C-peptide, and beta-hydroxybutyrate, along with a hypoglycemia agent screen, while hypoglycemia is occurring. If these data are not available from an episode of spontaneous hypoglycemia, a prolonged (72-hour) supervised fast is recommended to determine the cause of Whipple's triad. During a prolonged fast, approximately 100% of patients with an insulinoma will have Whipple's triad within 72 hours, 95% within 48 hours, and 67% within 24 hours. Approximately 85% of insulinomas are single benign tumors, 7% are multiple benign tumors, and 6% are malignant tumors.

Patients with NIPHS and PBH usually experience only postprandial hypoglycemia, especially after higher-carbohydrate foods, and do not generally have fasting hypoglycemia. An oral glucose tolerance test (OGTT) is not recommended to evaluate postprandial hypoglycemia because hypoglycemia occurs with similar frequencies in patients with hypoglycemic symptoms and in asymptomatic control patients. Also, an OGTT can cause significant dumping and severe hypoglycemia in patients with PBH. NIPHS and PBH are usually diagnosed by clinical presentation alone. A patient diary of symptoms and a continuous glucose monitor (CGM) may also be useful in detecting patterns of postprandial hyperglycemia followed by hypoglycemia. A mixed meal tolerance test (MMTT) is usually not necessary. During the MMTT, the patient consumes a solid or liquid meal similar in content to meals that usually provoke symptoms and is then observed for up to 5 hours. Plasma glucose, insulin, proinsulin, and C-peptide levels are obtained at baseline and every 30 minutes for 5 hours.

10. Describe PBH.

Hypoglycemia can sometimes occur after bariatric surgery (Roux-en-Y gastric bypass [RYGB], sleeve gastrectomy) and other procedures that alter the anatomy of the upper gastrointestinal tract (i.e., Nissen fundoplication). The prevalence of hospitalization due to PBH is reported to be 0.2% to 1.0%, although one-third of bariatric surgery patients responding to a mail survey reported hypoglycemic symptoms, with 11.6% reporting more serious symptoms, including needing third-party assistance. PBH is defined as postprandial hypoglycemia, often with neuroglycopenic symptoms that occurs at least 6 months after bariatric surgery despite adherence to an acceptable bariatric diet. There is a rapid rise in PG, often with values >180–200 mg/dL accompanied by a robust incretin (GLP-1 and GIP) and insulin response, leading to the development of hypoglycemia. Beta-cell suppression of insulin release and insulin clearance have also been found to be attenuated in PBH. In addition to insulin-mediated mechanisms, non–insulin-mediated factors are also involved in the pathogenesis, including a diminished counterregulatory hormone response, altered bile acid and serotonin metabolism, a transformed microbiome, and increased intestinal upregulation of glucose transporters.

11. How do you treat PBH?

Dietary modification is the gold standard for treatment. Patients are advised to eat a diet high in protein, to limit carbohydrates to only complex carbohydrates under 30 g per meal, and to limit added sugar to under 4 g per meal. If hypoglycemia persists after dietary modification, an alpha-glucosidase inhibitor, such as acarbose or miglitol, is often used. Alpha-glucosidase inhibitors impair carbohydrate absorption and thereby reduce the postprandial rise in glucose and insulin. Unfortunately, alpha-glucosidase inhibitors are often not tolerated, leading to bloating and gastrointestinal distress. Although data are limited, uncooked corn starch, GLP-1 agonists, somatostatin analogues, and diazoxide have been used with varying degrees of success. Although counterintuitive, since GLP-1 levels are elevated in PBH, GLP-1 agonist medications may reduce hypoglycemia by suppressing appetite and attenuating meal-induced endogenous GLP-1 peaks by steadily saturating GLP-1 receptors. Early studies showed promising results for avexitide, a GLP-1 antagonist, in reducing hypoglycemia, and phase 3 studies are currently underway. In addition, a selective SGLT-1 inhibitor, mizagliflozin, is being investigated as a possible treatment for PBH in phase 3 trials. In severe cases refractory to dietary modification and pharmacotherapy, options include reversal of the RYGB, surgical restoration of gastric restriction, and tube feeds through a gastrostomy tube inserted into the remnant stomach with no calorie intake by mouth. However, the success rate of approximately 70% with RYGB reversal is not ideal. Treatment with pancreatectomy has fallen out of favor due to high morbidity and incomplete resolution or recurrence of hypoglycemia.

12. What is NIPHS?

NIPHS is a very rare cause of endogenous hyperinsulinemic hypoglycemia presenting in adulthood. Affected patients have primarily postprandial hypoglycemia caused by islet cell hypertrophy. Pathologic findings (nesidioblastosis) are similar to those seen in neonates and infants with persistent hyperinsulinemic hypoglycemia and in adults with PBH. PBH and NIPHS have similar clinical presentations and pathologic findings, but NIPHS occurs in the absence of prior bariatric surgery and is classified as a separate entity.

13. How do you treat NIPHS?

The treatment for NIPHS and PBH are the same. Mild cases may respond to dietary modification alone. Simple carbohydrate consumption should be limited, and higher-protein and high-fiber diets are encouraged to blunt postprandial glucose and insulin excursions. Acarbose can also be added, if needed. Diazoxide, somatostatin analogues, and calcium channel blockers have also been used with varying degrees of success. In severe cases, a partial or rarely complete pancreatectomy may be necessary.

14. How do you distinguish an insulinoma from factitious hypoglycemia?

Insulinomas are characterized by hypoglycemia with elevated or inappropriately normal serum insulin, C-peptide, and proinsulin levels. Surreptitious insulin administration is identified by finding elevated serum insulin but low levels of C-peptide and proinsulin, because endogenous insulin secretion is suppressed in this situation. Circulating insulin antibodies may be positive with surreptitious insulin administration and with insulin autoimmune syndrome. However, patients with insulin autoimmune syndrome have elevated C-peptide and proinsulin levels. Surreptitious sulfonylurea or meglitinide ingestion is suggested by finding elevated serum insulin, C-peptide, and proinsulin levels with a positive drug screen for oral hypoglycemic agents.

15. What procedures are helpful to localize the cause of pancreatic islet cell hyperinsulinemia?

Once biochemical evidence of an insulinoma is confirmed, abdominal imagining should be the next step. Noninvasive imaging options include transabdominal ultrasonography, abdominal computed tomography (CT), and magnetic resonance imaging (MRI). A positron emission tomography (PET)/CT with ^{68}Ga-DOTA-exendin-4 can also help localize insulinomas. Some insulinomas are extremely small (less than a few millimeters) and easily escape detection on noninvasive imaging. Endoscopic ultrasonography may be useful in these cases. Selective arterial calcium infusions can also localize occult tumors and help distinguish between an isolated insulinoma and diffuse disease. Intraoperative ultrasonography is also useful for localizing pancreatic tumors.

16. If surgical resection of an insulinoma is not possible or the patient has metastatic or inoperable carcinoma, adenomatosis, or hyperplasia, what management options may control the hypoglycemia?

Dietary changes, such as frequent feedings and snacks, can be helpful. The most commonly used medication is diazoxide, which inhibits insulin secretion. Somatostatin analogues (octreotide, lanreotide, pasireotide), verapamil, and phenytoin can also be effective. Endoscopic ethanol ablation, radiofrequency ablation, and cryoablation have been used successfully in nonsurgical candidates and, therefore, are other options if there is sufficient expertise in this procedure available. For islet cell carcinoma, various chemotherapeutic agents can be used (see Chapter 61).

17. If other family members have pancreatic tumors, what condition is suggested?

Multiple endocrine neoplasia type 1 (MEN-1) occurs as an autosomal dominant condition characterized by functioning and nonfunctioning pituitary tumors, parathyroid hyperplasia, and islet cell tumors, most commonly gastrinomas (Zollinger-Ellison syndrome) and insulinomas. When this condition is suspected, family members should be screened genetically or tested for the components of MEN-1. However, only about 5% to 10% of insulinomas are associated with MEN-1 (see Chapter 60).

18. What are the causes of childhood hypoglycemia?

Hyperinsulinemic hypoglycemia in children can result from the same etiologies that cause this condition in adults, but persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is the most common cause of persistent hypoglycemia in infants. PHHI has also been referred to as *congenital hyperinsulinism, primary islet cell hypertrophy*, and *familial hyperinsulinemic hypoglycemia.* Nesidioblastosis, characterized by abnormal hypertrophied beta cells, is seen on pathologic examination of surgical specimens. Non–insulin-mediated hypoglycemia in infants and young children suggests an inborn error of metabolism, such as defective gluconeogenesis and/or glycogen metabolism (i.e., glycogen storage disease type 1 or glucose-6-phosphatase deficiency) or a fatty acid oxidation disorder. Adrenal insufficiency also causes non–insulin-mediated hypoglycemia in childhood.

19. What are the most common drugs that cause hypoglycemia in adults?

It is important to rule out insulin and oral insulin secretagogues (sulfonylureas, meglitinides) as the cause of hypoglycemia. Other drugs that have at least moderate quality of evidence supporting an association with hypoglycemia include indomethacin, quinine, pentamidine, quinolones, tramadol, and cibenzoline.

20. How does alcohol cause hypoglycemia?

Ethanol acutely inhibits hepatic gluconeogenesis. Hypoglycemia from alcohol ingestion generally occurs only in patients who also have impaired glycogenolysis caused by depletion of hepatic glycogen stores from fasting or chronic malnutrition. It is, therefore, the combination of acutely impaired gluconeogenesis and ineffective glycogenolysis that results in alcohol-induced hypoglycemia.

21. What is the mechanism of non–islet cell tumor hypoglycemia (NICTH)?

Hypoglycemia can occur most commonly with large mesenchymal or epithelial cell tumors, myelomas, fibromas, carcinoid tumors, colorectal carcinomas, and hepatocellular carcinomas. NICTH is an infrequent complication of malignancy and can be caused by various mechanisms. Most commonly, these tumors secrete incompletely processed insulin-like growth factor-2 (IGF-2) and rarely IGF-1, which bind to insulin receptors to cause hypoglycemia; therefore the insulin, pro-insulin, C-peptide, and beta-hydroxybutyrate levels are low when the hypoglycemia occurs. The IGF-2 to IGF-1 ratio is elevated above the normal molar ratio of 3:1 and is often 10:1 or higher. IGF-2 also suppresses growth hormone and glucagon. Thus, IGF-2 promotes continued glucose utilization and inhibits glycogenolysis and gluconeogenesis. Less commonly, non–islet cell tumors can produce insulin or insulin receptor antibodies. Treatment is surgical resection of the tumor, which usually resolves hypoglycemia. If total tumor resection is not feasible or “bridge” therapy is needed prior to resection, high-dose glucocorticoids equivalent to prednisone 30–60 mg/day are used. Other potential therapy includes dextrose infusion, diazoxide, glucagon infusion pumps, and recombinant growth hormone. Of note, hypoglycemia can also occur as a result of bilateral adrenal gland or liver destruction from widespread tumor invasion or metastases.

22. What autoimmune syndromes are associated with hypoglycemia?

Autoantibodies directed against insulin receptors or insulin itself may provoke hypoglycemia. Insulin receptor antibodies bind directly to and stimulate insulin receptors and thereby mimic insulin action in tissues. Insulin antibodies bind circulating insulin and randomly dissociate from insulin at inappropriate times, causing a sudden rise in free insulin levels and subsequent hypoglycemia. This disorder is observed most often in patients from Japan, where the condition may occur spontaneously. Other triggers for insulin autoimmune syndrome (IAS) are drug exposure (such as antithyroid medications and certain antibiotics), other autoimmune or hematologic conditions such as MGUS or multiple myeloma, and recent viral infection where super antigens activate insulin autoantibodies. IAS is often self-limiting, resolving in 3–6 months, especially if drug exposure is the cause and the drug is stopped. For severe cases, glucocorticoid treatment is often used. Other available treatments include pharmacotherapy that reduces pancreatic insulin secretion (such as somatostatin analogues and diazoxide), immunosuppressants (azathioprine and 6-mercaptopurine), monoclonal antibodies (rituximab), and plasma exchange to remove autoantibodies.

23. When is hypoglycemia attributed to underlying medical illness?

Patients with critical illness have multiple reasons for developing hypoglycemia, including hepatic dysfunction, renal insufficiency, medications, and poor dietary intake. Hepatic failure leads to hypoglycemia because of the liver’s role in gluconeogenesis and glycogenolysis. Renal failure causes hypoglycemia as a result of reduced renal clearance of insulin and decreased renal glucose production caused by impaired renal gluconeogenesis. During sepsis, elevated cytokines may increase glucose utilization and inhibit gluconeogenesis, causing hypoglycemia when glycogen stores are not sufficient. Starvation states, such as anorexia nervosa, also cause hypoglycemia as a result of depletion of glycogen stores and lack of substrate for gluconeogenesis.

KEY POINTS

- Hypoglycemia in a person without diabetes is defined by the presence of Whipple's triad.
- Obtaining fasting values for insulin, proinsulin, C-peptide, and beta-hydroxybutyrate along with a sulfonylurea screen while hypoglycemia is occurring is critical. If these data have not been acquired, a 72-hour supervised fast is recommended to determine the cause of Whipple's triad.
- If hyperinsulinemic hypoglycemia is present, a glucose rise of >25 mg/dL (1.4 mmol/L) is anticipated in response to the administration of intravenous glucagon, which acutely stimulates hepatic glycogenolysis.
- Hyperinsulinemic hypoglycemia suggests islet beta cell hyperfunction (insulinoma, noninsulinoma pancreatogenous hypoglycemia syndrome [NIPHS], or postbariatric hypoglycemia [PBH]), the surreptitious use of insulin or oral hypoglycemic agents, or insulin autoimmune hypoglycemia.
- Non–insulin-mediated hypoglycemia may be secondary to critical illness, starvation, alcohol abuse, adrenal insufficiency, non–islet cell tumors, glycogen storage diseases, or consumption of an unripe ackee fruit.

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Lipid Disorders

Timothy McGinnis and David R. Saxon

CHAPTER 11

1. What are the major lipids in the bloodstream?

Cholesterol and triglycerides (TGs) are the major circulating lipids. Cholesterol is used by all cells for the synthesis and repair of membranes and intracellular organelles and by the adrenal glands and gonads as a substrate to synthesize adrenal and gonadal steroid hormones. TGs are an energy source that can be stored as fat in adipose tissue or used as fuel by muscle and other tissues.

2. What are lipoproteins?

Cholesterol and TGs are not water soluble and thus cannot be transported through the circulation as individual molecules. Lipoproteins are large, spherical particles that package these lipids into a core surrounded by a shell of water-soluble proteins and phospholipids. Lipoproteins serve as vehicles that transport cholesterol and TGs from one part of the body to another.

3. What are the major lipoproteins in the bloodstream?

Chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) are the major circulating lipoproteins. Their functions are as follows:

Lipoprotein	Function
Chylomicron	Transport exogenous TGs from the gut to adipose tissue and muscle.
VLDL	Transport endogenous TGs from the liver to adipose tissue and muscle.
LDL	Transport cholesterol from the liver to peripheral tissues.
HDL	Transport cholesterol from peripheral tissues to the liver.

4. What are the apoproteins?

Apoproteins are located on the surface of the lipoproteins. They function as ligands for binding to lipoprotein receptors and as cofactors for metabolic enzymes. Their functions are as follows:

Apoprotein	Function
Apoprotein A	Ligand for peripheral HDL receptors
Apoprotein B	Ligand for peripheral LDL receptors
Apoprotein E	Ligand for hepatic receptors for remnant particles
Apoprotein C-II	Cofactor for lipoprotein lipase (LPL)

5. Name other enzymes and transport proteins that are important in lipoprotein metabolism.

See Table 11.1 and Fig. 11.1.

6. Describe the function and metabolism of LDL.

LDL transports cholesterol from the liver to peripheral tissues where surface apoprotein B-100 binds to cellular LDL receptors (LDLR). LDLR clustering in clathrin-coated pits on the cell membrane, promoted by LDLR adaptor protein 1 (LDLRAP1), is necessary for efficient LDL uptake. After LDL is internalized, it is degraded to free cholesterol (FC) for intracellular use. Excess LDL is cleared from the circulation by scavenger macrophages.

7. What is proprotein convertase subtilisin-like kexin type 9 (PCSK9)?

PCSK9 is a cellular protein that promotes the degradation of LDLR within lysosomes, thereby preventing recycling of the LDLR to the cell surface to internalize more LDL. Activating mutations of the gene for PCSK9 cause one rare form of familial hypercholesterolemia while

TABLE 11.1 Enzymes and Transport Proteins Important in Lipoprotein Metabolism

Enzyme/Protein Function	
ENZYME/TRANSPORT PROTEIN	**FUNCTION**
HMG CoA reductase	The rate-limiting enzyme in hepatic cholesterol synthesis
Lipoprotein lipase (LPL)	Removes TG from chylomicrons and VLDL in adipose tissue, leaving remnant particles
Hepatic lipase (HL)	Removes additional TG from remnant particles in the liver, converting them into LDL
Lecithin cholesterol acyl transferase (LCAT)	Esterifies cholesterol molecules on the surface of HDL, drawing them into the HDL core
Cholesterol ester transfer protein (CETP)	Shuttles esterified cholesterol back and forth between HDL and LDL
ATP citrate lyase	Generates acetyl-CoA from citrate for fatty acid and cholesterol biosynthesis

HDL, high-density lipoprotein; *LDL*, low-density lipoprotein; *TG*, triglycerides; *VLDL*, very-low-density lipoprotein.

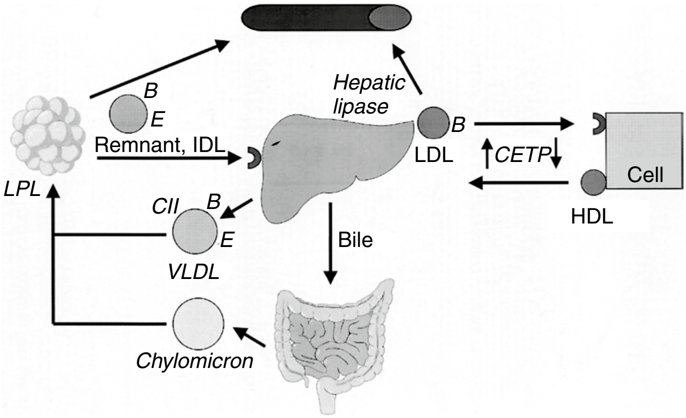

Fig. 11.1 Lipoprotein metabolism. B, Apolipoprotein B; CETP, cholesterol ester transfer protein; CII, apolipoprotein C-II; E, apolipoprotein E; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

inactivating mutations result in low serum LDL-C levels. This makes PCSK9 an interesting target for pharmacotherapy (see Question 31).

8. What is the function of HDL?

HDL removes excess cholesterol from cells by two mechanisms. Nascent pre-HDL is made in the liver and intestine. Surface Apo A1 on pre-HDL acquires free cholesterol (FC) through the ATP-binding cassette transporter A1 (ABCA1) on arterial wall macrophages. Plasma lecithin cholesterol acyl transferase (LCAT) then esterifies the FC to cholesterol ester (CE), forming a mature HDL particle. Mature HDL accepts additional FC from arterial macrophages through the ABCG1 transporter and the scavenger receptor, class B, type 1 (SR-B1) receptor. Cholesterol ester transfer protein (CETP) transfers some CE back to LDL particles, and the mature HDL transports the remaining CE to the liver, where transfer occurs through hepatic SR-B1 receptors. In addition to reverse cholesterol transport, HDL also reduces LDL oxidation, inhibits vascular inflammation, and improves endothelial function. All of these functions make HDL a potent antiatherogenic lipoprotein.

9. Describe the pathogenesis of the atherosclerotic plaque and arterial thrombosis.

LDL can be modified by oxidation. Scavenger macrophages located beneath the intimal surface of arteries engulf oxidized LDL, becoming lipid-laden foam cells, which secrete growth factors that stimulate smooth muscle cell proliferation. These developing plaques also secrete cytokines that attract inflammatory cells, which secrete proteolytic enzymes that erode the fibromuscular plaque cap, making it prone to rupture. When rupture occurs, platelets aggregate and release chemicals that promote vasoconstriction and initiate thrombus formation, which may ultimately occlude the artery.

10. Explain the function and metabolism of TGs.

Food and hepatic synthesis are the major sources of TGs. They are transported by chylomicrons (dietary TGs) and VLDL (endogenous TGs) to adipose tissue and muscle, where LPL and cofactor apoprotein C-II break down TGs into fatty acids (FAs) and monoglycerides. FAs enter adipose cells to be stored as fat or muscle cells to be used as fuel. The chylomicron and VLDL remnant particles return to the liver, where HL converts VLDL remnants into LDL.

11. Are elevated serum TG levels harmful?

Increased serum TG levels are associated with atherosclerosis and increased coronary disease. The American Heart Association states that triglycerides are not directly atherogenic but represent an important biomarker of cardiovascular risk because of their association with an atherogenic lipid profile (low HDL cholesterol levels and small, dense LDL particles), as well as obesity, insulin resistance, and the metabolic syndrome. It has not yet been shown that decreasing TG levels will decrease coronary disease risk. TG values greater than 1000 mg/dL significantly increase the risk of developing acute pancreatitis.

12. What is lipoprotein(a)?

Lipoprotein(a), often shortened to Lp(a), is an independent risk factor for atherosclerosis. When an apoprotein(a) molecule attaches to apoprotein B on the surface of an LDL particle, the new particle is referred to as lipoprotein(a). Excessive Lp(a) promotes atherosclerosis, possibly because it is easily oxidized and engulfed by macrophages, because it inhibits thrombolysis, or both. Lp(a) is also pro-thrombotic and has approximately 85% amino-acid sequence homology with plasminogen. Although certain medications can lower Lp(a) to an extent, no targeted treatments for this particle currently exist. Several medications that lower Lp(a) by >80% are currently being tested in phase 3 clinical trials.

13. What are the primary dyslipidemias?

Primary dyslipidemias are inherited disorders of lipoprotein metabolism. The major primary dyslipidemias and their lipid phenotypes are as follows:

Primary Dyslipidemia	*Phenotype*
Familial hypercholesterolemia (FH)	↑↑ Cholesterol
Polygenic hypercholesterolemia	↑ Cholesterol
Familial combined hyperlipidemia (FCH)	↑ Cholesterol and ↑ TGs
Familial dysbetalipoproteinemia (FDL)	↑ Cholesterol and ↑ TGs
Familial hypertriglyceridemia (FHT)	↑ TGs
Familial hyperchylomicronemia (FHC)	↑↑ TGs

14. What is familial hypercholesterolemia (FH)?

FH is an inherited disease characterized by extreme elevations of serum cholesterol but normal serum TG levels. The population frequency is 1:250 for heterozygous FH (HeFH), which generally presents with serum cholesterol levels of 300 to 800 mg/dL, and 1:1,000,000 for homozygous FH (HoFH), which results in serum cholesterol levels of 600 to >1000 mg/dL. Most patients have genetic mutations resulting in deficient or dysfunctional LDL receptors (LDLR). Other, less common monogenic hypercholesterolemic disorders include apoprotein B mutations that produce a defective apoB that cannot bind to LDLR, PCSK9 mutations that cause accelerated LDLR degradation, LDLR adaptor protein 1 (LDLRAP1) mutations that prevent normal clustering of LDLR in cell surface clathrin-coated pits, and ATP-binding cassette G5 or G8 (ABCG5/8) mutations that cause abnormal cellular transport of cholesterol and plant sterols (sitosterolemia). These disorders are characterized by premature coronary artery disease (CAD), often before the age of 20 in HoFH, and tendon xanthomas.

15. What is familial combined hyperlipidemia (FCH)?

FCH is an inherited disorder characterized by variable elevations of both serum cholesterol and TG levels. Affected patients have excessive hepatic apoprotein B synthesis, with increased numbers of apoprotein B containing VLDL and LDL particles. These people are prone to develop premature CAD. It most likely has a genetically complex basis, with the phenotype resulting from the interaction of the environment and multiple susceptibility genes.

16. What is familial dysbetalipoproteinemia (FDL)?

FDL is also known as broad beta disease, remnant removal disease, or type III hyperlipoproteinemia. It is an inherited condition characterized by increased serum total cholesterol, moderate hypertriglyceridemia (300–400 mg/dL), and normal HDL-C levels. This disorder stems from an abnormal apoprotein E phenotype (E2/E2), which binds poorly to hepatic receptors, resulting in impaired clearance of circulating VLDL remnants by the liver. Affected patients often develop premature CAD. Planar xanthomas in the creases of the palms and soles of the feet are a characteristic finding in patients with FDL.

17. What is polygenic hypercholesterolemia?

Polygenic hypercholesterolemia, which is characterized by mild-to-moderate elevations of serum cholesterol alone, is the most common type of inherited hypercholesterolemia. This condition generally occurs when one or more mild defects of cholesterol metabolism combine to elevate the serum cholesterol level. Affected patients have an increased risk of developing CAD.

18. What is familial chylomicronemia syndrome (FCS)?

FCS is characterized by extremely high serum TG and chylomicron levels. It is due to inactivating mutations in the gene for lipoprotein lipase (LPL), apolipoprotein C-II, apolipoprotein A-V, and lipase maturation factor 1. Severe hypertriglyceridemia with chylomicronemia predisposes to the development of eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and acute pancreatitis.

19. How do you distinguish between familial combined hyperlipidemia (FCH) and familial dysbetalipoproteinemia (FDL)?

Because FCH and FDL are characterized by combined elevations of both cholesterol and TGs, additional tests may be necessary to make the distinction. Patients with FCH have increased serum apolipoprotein B levels, whereas patients with FDL have an E2/E2 genotype and a broad beta-band on lipoprotein electrophoresis. Family studies are also helpful.

20. What causes familial low HDL-C?

Familial hypoalphalipoproteinemia (familial low HDL) is characterized by extremely low serum HDL-C levels (<5–10 mg/dL) and premature CAD. It is caused by inactivating mutations in the genes that encode apolipoprotein A1 (APOA1), ABCA1, or LCAT.LPL mutations reduce HDL-C to a lesser degree.

21. What causes elevated HDL-C?

Hyperalphalipoproteinemia (high HDL-C) is characterized by an HDL-C >80 mg/dL. Genetic mutations that lead to deficiencies of CETP, hepatic lipase, and APO-CIII have been shown to increase HDL-C. Increased estrogen levels raise HDL-C. Medications, including lipid-lowering agents (fibrates, niacin, statins) and antiinflammatory medications (NSAIDs, methotrexate, sulfasalazine, hydroxychloroquine), can increase HDL-C. Additionally, chronic alcohol use and liver disease can increase HDL-C.

Traditionally, elevated HDL-C levels have been thought of as protective against CVD. However, recent data suggest that very high HDL-C levels (>80 mg/dL) are associated with an increased risk of all-cause mortality and cardiovascular death in people with CAD compared to HDL-C levels of 40–60 mg/dL.

22. Name the secondary dyslipidemias.

The secondary dyslipidemias are serum lipid elevations that result from systemic diseases, such as diabetes mellitus, hypothyroidism, nephrotic syndrome, renal disease, obstructive liver disease, dysproteinemias, and lipodystrophies. Lipids also may be increased by medications, such as beta-blockers, thiazide diuretics, estrogens, progestins, androgens, retinoids, corticosteroids, cyclosporin A, antipsychotics, and protease inhibitors. These disorders usually improve when the primary condition is treated or the offending drugs are discontinued.

23. What are causes of acquired hypertriglyceridemia?

Hypertriglyceridemia can be caused by insulin resistance or obesity, other medical conditions (diabetes, HIV infection, nephrotic syndrome, hypothyroidism, connective tissue disease), alcohol use, and medications (estrogens, glucocorticoids, HIV medications, retinoids, some antihypertensive medications).

KEY POINTS

1. Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for coronary artery disease (CAD).
2. Low high-density lipoprotein cholesterol (HDL-C) is also a significant risk factor for CAD.
3. High serum triglycerides (TGs) are associated with increased CAD, but it is unclear whether lowering TG levels decreases CAD risk.
4. Serum TG levels >1000 mg/dL significantly increase the risk of developing acute pancreatitis.
5. Inflammation within the atherosclerotic plaque plays a major role in plaque rupture and the occurrence of acute coronary events.

24. Describe the general approach to the treatment of dyslipidemias.

Management of dyslipidemias usually requires a multifaceted approach and may include treatment of secondary causes, lifestyle changes, medical therapy, and rarely lipid apheresis.

25. What are the American College of Cardiology / American Heart Association (ACC/AHA) recommendations for lifestyle changes to improve atherosclerotic cardiovascular disease (ASCVD) risk?

For individuals who would benefit from LDL-C cholesterol lowering, the ACC/AHA guidelines recommend:

- Consuming a dietary pattern that emphasizes vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats. This can be achieved by following diet plans such as the DASH diet.
- Aiming for 5–6% of calories from saturated fats
- Reducing the percent of calories from saturated fats and *trans* fats.

26. What medications are currently available for treatment of dyslipidemias?

See Tables 112 and 113.

27. When does the ACC/AHA recommend treatment with medication for hypercholesterolemia?

The 2018 multisociety cholesterol guidelines recommend treating specific groups of individuals with high ASCVD risk. These groups include people with:

1. Clinical ASCVD
2. LDL ≥190 mg/dL
3. LDL = 70–189 mg/dL, diabetes, age 40–75 years
4. LDL = 70–189 mg/dL, no diabetes, age 40–75 years, 10-year ASCVD risk ≥7.5%

For individuals over age 75, risks and benefits should be discussed to allow for shared decision-making. In addition, risks and benefits should be discussed with younger individuals <40 years of age with high ASCVD risk.

28. What are the risk enhancing factors that should be considered when considering treatment with lipid-lowering medications?

In people with borderline (5–7.4%) or intermediate (7.5–19.9%) ASCVD risk the presence of certain risk-enhancing features should prompt initiation or intensification of statin therapy. These include history of preeclampsia, early menopause, rheumatologic disease, HIV, strong family history of coronary heart disease, South Asian ancestry, chronic kidney

TABLE 11.2 Available Medications for Treatment of Lipid Disorders

	AVAILABLE AGENTS	LDL-C EFFECT (%)	TG EFFECT (%)	HDL-C EFFECT (%)
Statins	Rosuvastatin Atorvastatin Pitavastatin Simvastatin Pravastatin Lovastatin Fluvastatin	↓ 20–60	↓ 0–30	↑ 0–15
Cholesterol absorption inhibitors	Ezetimibe	↓ 18–25	None	↓ 5–10
PCSK9 inhibitor: monoclonal antibodies	Alirocumab Evolocumab	↓ 30–70	↓ 0–25	↑ 5–10
PCSK9 inhibitor: siRNA	Inclisiran	↓ 30–50	↓ 5–10	↑ 5–10
ATP citrate lyase inhibitor	Bempedoic acid	↓ 15–30	Slight decrease–slight increase	↓ 5–10
ANGPTL3 inhibitor	Evinacumab	↓ 50	↓ 50	↓ 30–35
Bile acid sequestrants	Cholestyramine Colestipol Colesevelam	↓ 15–30	None or slight increase	None or slight increase
Nicotinic acid	Niacin Niacin ER	↓ 10–25	↓ 25–30	↑ 15–35
Fibrates	Fenofibrate Gemfibrozil	↓ 0–20; can increase	↓ 30–45	↑ 5–10
Omega 3 fatty acids	EPA DHA	↑ 0–10	↓ 20–50	↑ 5–10

DHA, docosahezaenoic acid; *EPA*, eicosapentaenoic acid; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglycerides; *VLDL*, very-low-density lipoprotein.

TABLE 11.3 Statin Intensity Chart

HIGH INTENSITY	MODERATE INTENSITY	LOW INTENSITY
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Simvastatin 10–20 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

disease, persistently elevated triglyceride levels, low ankle-branchial index, high CRP, high lipoprotein(a) or apolipoprotein B.

29. Describe the mechanism of action of statin medications.

Statins inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA reductase), the rate-limiting enzyme in cholesterol synthesis. This leads to a decrease in cholesterol synthesis and an increase in hepatic LDL receptor-mediated LDL removal from the circulation. The available statins are fluvastatin, pravastatin, lovastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin. Atorvastatin 40 mg and 80 mg, and rosuvastatin 20 mg and 40 mg are considered high-potency statins. Each subsequent doubling of the statin dose will, on average, result only in an additional 6% decrease in serum LDL-C.

30. What are potential side effects of statins?

Myalgias occur in 5–15% of people who take statins. True myositis is much less common, and rhabdomyolysis is very rare (approximately 1:10,000). For creatine kinase (CK) elevations greater than five times the upper limit of normal or if the person has moderate to severe symptoms, the statin should be stopped. Once the person is asymptomatic and the CK is reduced, reasonable approaches include a trial of low-dose fluvastatin or pravastatin, alternate daily or weekly dosage of a more potent statin such as rosuvastatin or pitavastatin, or combination of a low-dose statin with a nonstatin cholesterol agent (ezetimibe or bile acid sequestrant). Over-the-counter preparations containing natural statin-like agents, such as red yeast rice, can also be tried, although they undergo limited quality control and have low efficacy. For people with mild symptoms and CK elevations less than five times the upper limit of normal, the statin may be continued. If symptoms worsen, then the CK should be rechecked.

There have also been concerns about increased rates of memory loss with statins. However, blinded studies do not show higher rates of myalgias or memory loss. Statins do slightly increase the risk of metabolic syndrome, prediabetes, and diabetes, as was shown in the JUPITER trial.

31. Does aggressive cholesterol lowering therapy effectively and safely reduce the risk of coronary artery disease?

Clinical trials have repeatedly demonstrated the efficacy of aggressive cholesterol lowering with statins in reducing myocardial infarction, strokes, and cardiovascular mortality in people with a previous history of CAD (secondary prevention). A meta-analysis from the Cholesterol Treatment Trialists' Collaboration suggests that each 1 mmol/L (38.7 mg/dl) reduction in LDL-C results in an approximately 20% reduction in the annual rate of cardiovascular disease events.

The role of statins in the setting of primary prevention is less clear. While trials have shown that LDL-C reduction with medical therapy decreases the rate of CVD events and CVD mortality, the effects on all-cause mortality remain uncertain. In addition, the cost effectiveness of statins and the overall effect on quality of life in the setting of primary prevention is unclear. Therefore a risk stratification approach, as advocated in the guidelines, is most prudent.

32. What is the appropriate role for ezetimibe?

Ezetimibe, which inhibits intestinal cholesterol absorption, lowers LDL-C by 17–20% when used as monotherapy. It is somewhat more effective when used in combination with statins, lowering LDL-C by 25%. Ezetimibe added to statin therapy in high-risk individuals has modest effects on ASCVD events.

33. Describe the available PCSK9 inhibitors.

There are two subclasses of PCSK9 inhibitors currently approved in the United States Evolocumab and alirocumab are monoclonal antibodies to PCSK9 that prevent the binding of PCSK9 to the LDL-LDLR complex. This causes increased recycling of LDLR to the cell membrane and enhanced LDL clearance with reductions in LDL-C levels of 50–70%. Cardiovascular event reduction has also been demonstrated in several large randomized controlled trials (RCTs). Inclisiran, a PCSK9 mRNA inhibitor, represents a second subclass of PCSK9 inhibitor that is administered every 6 months and results in approximately 50% reductions in LDL-C.

34. What is bempedoic acid?

Bempedoic acid is an oral pro-drug that requires activation by ACSVL1, which is absent in skeletal muscle, thereby causing less myotoxicity than statins. It lowers LDL-C by approximately 20% when used alone and by approximately 40% in a combination pill with ezetimibe. Side effects include an increased risk of gout, elevated liver enzymes, nasopharyngitis, and tendon rupture.

35. What other aggressive therapies are available for familial hypercholesterolemia (FH)?

Mipomersen is an antisense oligonucleotide Apo B inhibitor; it lowers LDL-C approximately 25–38%. Lomitapide is a microsomal triglyceride transfer protein inhibitor; it lowers LDL-C approximately 40–50%. These two medications can have significant hepatotoxicity and are very expensive; furthermore, neither medication has been shown to reduce cardiovascular events. As a result, they are seldom used but are available in limited circumstances. LDL apheresis lowers LDL-C by 70–80% and has been shown to reduce cardiovascular events and improve quality of life. This modality is available mainly in specialty centers and is used when combination therapy with statins and PCSK9 inhibitors is insufficiently effective or can't be used.

36. What is evinacumab?

Evinacumab is a monoclonal antibody against ANGPTL3, a protein that inhibits lipoprotein lipase and endothelial lipase (leading to increased lipids). The medication reduces LDL-C by approximately 50% and is currently only FDA approved for use in homozygous familial hypercholesterolemia.

37. What is lipoprotein apheresis?

Lipoprotein apheresis, also known as LDL apheresis, is the selective removal of LDL-C and Lp(a) from plasma. Lipid apheresis is used primarily in familial hypercholesteremia (FH). Current FDA-approved indications include homozygous FH with LDL-C ≥500 mg/dL, heterozygous FH with LDL-C ≥300 mg/dL, heterozygous FH with ASCVD when LDL ≥100 mg/dL, and ASCVD with elevated Lp(a) ≥60 mg/dL.

38. How should the patient with severe hypertriglyceridemia be managed?

Serum TG levels above 1000 mg/dL must be lowered quickly because of the high risk of precipitating acute pancreatitis. Medications alone are not effective when TG levels are this high. Patients must immediately be placed on a very-low-fat (less than 5% fat) diet until the TG level is less than 1000 mg/dL. Such a diet lowers serum TGs approximately 20% each day. Contributing factors—most commonly uncontrolled diabetes mellitus, alcohol use disorder, estrogen use, and HIV medications—must simultaneously be addressed. After serum TG levels are less than 1000 mg/dL, the most effective medications to reduce serum TGs further are the fibrates. If these medications do not lower serum TG sufficiently, niacin, fish oils, or a statin may be added to the regimen.

39. What is the appropriate role for fibrates?

Fibrates, which decrease VLDL production, are the most effective TG lowering agents. They also increase HDL-C and modestly decrease LDL-C. While they can reduce LDL-C modestly in some patients without hypertriglyceridemia, and in those with familial dysbetaliproteinemia they are not a first-line therapy for treating isolated elevations in LDL-C and should be thought of as primarily a treatment for hypertriglyceridemia.

40. What is icosapent ethyl and what is its role in CVD risk reduction?

Icosapent ethyl is a highly purified eicosapentaenoic acid, which is a type of omega-3 fatty acid. It lowers triglyceride levels and has also been shown to decreased CVD risk, possibly through its antiinflammatory, antioxidative, cholesterol membrane stabilizing, and plaque-stabilizing effects. The REDUCE-IT trial demonstrated that icosapent ethyl had a 25% RRR in cardiovascular death, nonfatal MI, and nonfatal stroke compared to placebo.

However, other omega-3 fatty acid trials have not shown similar effects in ASCVD risk reduction. Particularly, the STRENGTH and OMEMI trials found no significant difference in CVD risk reduction between the trial medications (omega-3 fatty acid derivatives) and placebo. One theory for the differences between the trials is that the REDUCE-IT trial used mineral oil as the placebo and the STRENGTH trial used corn oil. Mineral oil increases CRP and LDL levels more than corn oil, which could explain the increased RRR seen in the REDUCE-IT trial. Further studies may be warranted to determine the true effect that icosapent ethyl has on CVD risk reduction.

KEY POINTS

Treatment of Lipid Disorders

1. Statins are first-line LDL cholesterol-lowering agents that have the strongest evidence base for reducing cardiovascular events.
2. PCSK9 inhibitors are also potent LDL-C reducers, and there is evidence for cardiovascular event reduction, but their use is currently limited by high cost.
3. Additional LDL-C reduction can be achieved by adding ezetimibe, niacin, and bile acid resins.
4. Fibrates are the most effective TG-lowering agents; additional reductions can be achieved by adding niacin, fish oils, and high-dose statins.
5. Management of dyslipidemias usually requires a multifaceted approach and may include treatment of secondary causes, lifestyle changes, medical therapy, and, rarely, apheresis.

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CHAPTER 12

Obesity

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1. Define the terms "overweight" and "obesity."

Overweight and obesity are defined as degrees of excess weight that are associated with increases in morbidity and mortality. In 1998, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) published guidelines on the diagnosis and treatment of overweight and obesity. The expert panel advocated using specific body mass index (BMI) cutoff points to diagnose both conditions. The BMI is calculated by dividing a person's weight in kilograms by his or her height in meters squared. The World Health Organization (WHO) defines overweight and obesity in four different classes: preobesity (BMI 25.0–29.9 kg/m^2), class I obesity (BMI 30.0–34.9 kg/m^2), class II obesity (BMI 35.0–39.9 kg/m^2), and class III obesity (BMI ≥40.0 kg/m^2).

2. Does fat distribution affect the assessment of risk in the patient with overweight or obesity?

Accumulation of excessive adipose tissue in a central- or upper-body distribution (android or "apple" shaped) is associated with a greater risk of adverse metabolic health consequences than lower-body obesity (gynoid or "pear" shaped). Abdominal adiposity is an independent predictor of risk for diabetes, hypertension, dyslipidemia, and coronary artery disease. The absolute amount of intra-abdominal or visceral fat is most closely linked to these adverse health risks.

3. Explain the role of waist circumference in risk stratification.

Waist circumference is the favored measure for risk stratification in patients with obesity because it directly assesses fat distribution. Men with a waist circumference greater than 40 inches (>102 cm) and women whose waist circumference is greater than 35 inches (>88 cm) have increased risks of cardiometabolic comorbidities. Waist circumference is most useful for risk stratification in people with a BMI between 25 and 30 kg/m^2. In this intermediate-risk group, those with increased waist circumference should undertake greater efforts directed at preventing further weight gain.

4. How is waist circumference measured?

Waist circumference should be measured with a tape measure parallel to the floor at the level of the iliac crest at the end of a relaxed expiration.

5. What adverse health consequences are associated with obesity?

Obesity is clearly associated with diabetes, hypertension, hyperlipidemia, coronary artery disease, degenerative arthritis, gallbladder disease, and cancer of the endometrium, breast, prostate, and colon. It has also been associated with urinary incontinence, gastroesophageal reflux, infertility, sleep apnea, and congestive heart failure. The incidence of these conditions rises steadily as body weight increases. Risks increase with even modest weight gain. Health risks are magnified with advancing age and a positive family history of obesity-related diseases.

6. Summarize the economic consequences of obesity.

The total direct U.S. health care costs associated with obesity were estimated to exceed $173 billion annually in 2022. Much of the cost of obesity is due to the high cost of treating obesity-related comorbidities such as cardiovascular disease and type 2 diabetes.

7. What are the psychological complications of obesity?

Situational depression and anxiety related to obesity are common. Persons with obesity may suffer from discrimination that contributes further to difficulty with poor self-image and social isolation. It may be difficult for some patients to determine whether depression is accelerating weight gain or whether weight gain is exacerbating an underlying depression, but treating both conditions may improve quality of life. Work by the Rudd Center and other groups has highlighted the bias that patients with obesity experience even from doctors who care for them. It is important for treating physicians to be aware of the tendency to blame patients with obesity for their condition and to compensate for this common bias.

8. How common is obesity?

Obesity has reached epidemic proportions in the United States. The National Health and Nutrition Examination Survey (NHANES) conducted by the federal government uses direct measures of height and weight in a representative sample of Americans to estimate the prevalence of obesity. The latest data from the NHANES showed that in 2017–2018, the prevalence of obesity was >33% in adults and 20% in youth. The overall prevalence of obesity is higher among non-Hispanic black and Hispanic adults than among non-Hispanic white and non-Hispanic Asian adults. It is projected that by the year 2030, 50% of adults in the United States will have obesity, and that 25% will have class II or greater obesity. Class II and III obesity (BMI $\geq$35.0 kg/m^2) is predicted to be the most common BMI category for women, black adults, and adults of low socioeconomic status.

9. Describe the current model for obesity as a chronic disease.

Obesity is now viewed as a chronic, often progressive metabolic disease much like diabetes or hypertension. This view requires a conceptual shift from the previous widely held belief that obesity is simply a cosmetic or behavioral problem. The development of obesity requires a period of positive energy balance during which energy intake exceeds energy expenditure. Maintaining energy balance is one of the most important survival mechanisms of any organism. A sustained negative imbalance between energy intake and expenditure is potentially life threatening within a relatively short time. To maintain energy balance, the organism must assess energy stores within the body, assess the nutrient content of the diet, determine whether the body is in negative energy or nutrient balance, and adjust hormone levels, energy expenditure, nutrient movement, and eating behavior in response to these assessments.

10. Do abnormal genes cause obesity?

Obesity is clearly more common in people who have family members who are also obese. Genetics appears to be responsible for 30% to 60% of the variance in weight in most populations. The problem of human obesity, however, involves an interaction between genetic susceptibility and environmental triggers. The genes that we possess to regulate body weight evolved somewhere between 200,000 and 1 million years ago, at which time the environmental factors controlling nutrient acquisition and habitual physical activity were dramatically different. Several single-gene defects have been identified that cause severe obesity presenting in childhood: leptin, leptin receptor, melanocortin 4 receptor (MC4-R), proopiomelanocortin (POMC), brain-derived neurotrophic factor, and others. However, these mutations are quite rare, explaining <8% of severe early-onset obesity. Genome wide association studies have identified >20 genes that are associated with common forms of human obesity. The most common of these is the *FTO* gene. The allele of this gene that is associated with weight gain is present in 15% of humans. However, the weight gain associated with this high-risk allele is only 3 kg. Thus, common human obesity appears to be the result of alterations in many genes, each having relatively small effects (polygenic).

11. What is leptin?

Leptin is a hormone secreted exclusively by adipose tissue in direct proportion to fat mass. It was discovered in 1994. Leptin acts through receptors located on neurons in the arcuate nucleus of the hypothalamus and other brain regions to regulate both food intake and energy expenditure. Changes in leptin levels in the hypothalamus alter the production of several neuropeptides including POMC and agouti-related peptide (AGRP).

12. Does leptin deficiency cause human obesity?

There are a handful of cases in which genetic deficiency of leptin, or its receptor, have been found to cause severe early-onset obesity. Treating leptin-deficient humans with leptin results in dramatic weight loss. However, leptin levels are typically increased in people with obesity compared with lean humans in proportion to their increased fat mass. Studies in which recombinant human leptin was administered to patients with obesity produced minimal weight loss. These findings suggest that common forms of human obesity are associated with leptin resistance, not leptin deficiency.

13. Explain how the melanocortin system is involved in weight regulation.

Alpha-melanocortin (α-MSH) is one of the hormone products of the POMC gene. This neuropeptide acts in the hypothalamus on melanocortin receptors, particularly the MC4-R subtype, to regulate body weight. By stimulating the MC4-R, α-MSH inhibits food intake, whereas the natural antagonist AGRP, also made in the hypothalamus, stimulates food intake. MC4-R agonists have been developed. While these drugs decrease food intake and reduce body weight in obese rodents, they have not been found to be useful as single agents in patients with obesity. The failure of these drugs and others that work through hypothalamic regulatory pathways to produce significant weight loss in patients with obesity has raised questions as to the role of these systems in common forms of human obesity.

14. What is ghrelin?

Ghrelin is a hormone originally identified as a growth hormone-releasing hormone produced by the stomach and proximal small intestine that appears to regulate appetite. Ghrelin levels rise before meals and promptly fall following food intake. Self-reported hunger mirrors serum ghrelin levels. Twenty-four-hour ghrelin levels rise when people go on an energy-restricted diet and are dramatically reduced after gastric bypass surgery. Ghrelin has been described as a “hunger hormone” and is another possible target for weight loss drugs. The bioactive form of the hormone, acylated ghrelin, has a fatty acid attached to the parent hormone. Drugs that alter the production of acylated ghrelin are also being investigated.

15. Explain the concept of energy balance.

When an individual’s weight is stable, total daily energy expenditure equals total daily energy intake. Total energy expenditure is linearly related to lean body mass. Studies that have used sophisticated methods for measuring energy expenditure have clearly shown that people with obesity consume more calories than lean people. People with obesity who say that they eat only a small amount but are gaining weight may be telling the truth in the short term, but over longer periods high caloric intakes are required to maintain the obese state. Although reduced levels of physical activity energy expenditure (PAEE) may predispose to obesity, basal metaboic rate (BMR) is not reduced in people with obesity. The central cause of obesity is the failure to match energy intake to energy expenditure accurately over time.

16. Does a decrease in energy expenditure play a role in the development of obesity?

The development of obesity requires an imbalance between caloric intake and caloric expenditure. For fat mass to increase, there must be an imbalance between the amount of fat deposited compared with the amount of fat oxidized. One possibility is that people become obese because of a reduction in their energy expenditure. Despite the common idea that a “low metabolic rate” predisposes to obesity, there is little evidence that this is true.

17. What are the components of energy expenditure?

1. Basal metabolic rate (BMR): The amount of energy needed to maintain body homeostasis by maintaining body temperature, cardiopulmonary integrity, and electrolyte stability.
2. Thermic effect of food: A relatively small component (5% to 10%) that represents the energy cost associated with the digestion of a meal.
3. Physical activity energy expenditure (PAEE): This is the most variable component. It can account for as little as 10% to 20% of total energy expenditure in people who are sedentary or as much as 60% to 80% of total energy expenditure in training athletes. PAEE increases with planned physical activity or with activities of daily living, such as stair climbing or even fidgeting. The unconscious component of physical activity has been termed *nonexercise activity thermogenesis* (NEAT) and may be a regulated parameter.

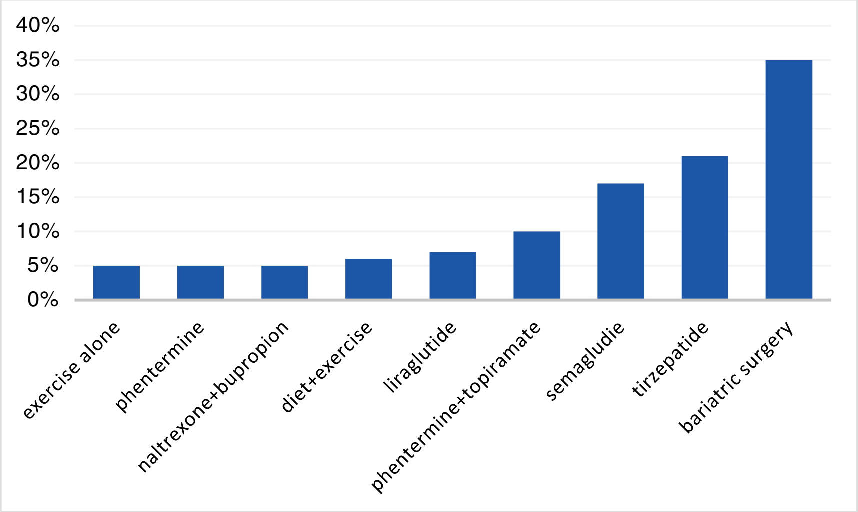

Fig. 12.1 Average weight loss produced by the maximum doses of each anti-obesity treatment.

18. Are there other factors involved in the increase in the prevalence of obesity?

Investigators have identified a range of novel environmental factors that may be related to the increase in obesity seen over the last 40 years. One area that has received a good deal of attention is reduced sleep time. On average, Americans are sleeping less than they did 50 years ago. Epidemiological studies have shown that shortened sleep time is associated with obesity, and experimental studies have shown that sleep restriction is associated with insulin resistance, increased appetite, and a change in fat oxidation. Medication use is another factor that may be involved in promoting obesity. Widely used medications that promote weight gain include steroids, antipsychotic medications, sulfonylureas, insulin, thiazolidinediones, and progesterone-containing birth control medications.

19. What options are available for treating patients with obesity?

Treatment options for people with overweight or obesity include diet, exercise, pharmacotherapy, surgery, and combinations of these modalities (Fig. 12.1). The specific modality should be based on the individual's BMI and their associated health problems. A more aggressive treatment approach is warranted in those whose BMI is higher and those with weight-related health problems. Behavioral approaches such as physical activity and healthy eating habits should be a part of the treatment plan for all patients regardless of weight but are critical for patients with overweight and obesity. Pharmacologic treatment should be considered in those whose BMI is greater than 27 kg/m^2 in the presence of medical complications or greater than 30 kg/m^2 in the absence of medical complications. Surgical treatment is currently reserved for those with a BMI greater than 40 kg/m^2, or a BMI greater than 35 kg/m^2 with comorbidities. Recent evidence suggests that bariatric surgery is also helpful for patients with diabetes whose BMI is less than 35 kg/m^2.

20. What is the goal of a weight loss program?

Before discussing the treatment options with a patient, it is important to decide the goal of the treatment program. Many patients with obesity have unrealistic expectations about the amount of weight they might lose through a weight loss program. Most would like to achieve ideal body weight and are disappointed if they lose only 5% to 10% of their initial weight. These desires stand in stark contrast to the magnitude of weight loss that has been seen with all treatment modalities short of bariatric surgery and some pharmacotherapies. The most effective diet and exercise programs result in a maximum of 5–10% weight loss in most people.

21. Is a 5% to 10% reduction helpful in terms of health improvement?

This degree of weight reduction has been associated with improvements in health-related measures, such as lower blood pressure, reductions in low-density lipoprotein (LDL) cholesterol levels, improved functional capacity, and a markedly reduced risk of developing diabetes. Most experts now believe that a sustained 5% to 10% weight loss is a realistic goal with measurable health benefits. Alternatively, prevention of further weight gain may be a reasonable and attainable goal, or the health care provider may simply encourage the patient to focus on healthy eating and activity habits and not on a weight goal at all.

22. How can a patient's readiness to change his or her diet or physical activity be assessed?

Stages of change theory can help the clinician focus counseling activities within the context of a brief office visit. Prochazka has hypothesized six predictable stages through which a person passes before he or she is able to change long-standing behaviors such as diet, physical activity patterns, or smoking: precontemplative, contemplative, planning, action, maintenance, and relapse. Identifying the stage that the patient is in and targeting counseling efforts to that stage may improve the effectiveness of the counseling activities.

23. What is motivational interviewing, and how is it used in counseling a patient with obesity?

Motivational interviewing is a counseling style that was developed for use with patients with alcohol use disorders. The method is useful when interacting with patients who are ambivalent about changing their diet or physical activity behaviors. The strategies used focus on resolving this ambivalence by having patients explore reasons why they want to change and reasons why they find their current behavior more comfortable. The method grows out of the idea that motivation cannot be created, but for many patients the motivation is already there—it simply needs to be identified and redirected.

24. Discuss the role of diet in the treatment of patients with obesity.

The mainstays of dietary modification in weight loss therapy have been diets low in fat and reduced in calories; however, studies have shown that no single specific diet is superior to all others. Compelling evidence in favor of this approach comes from the Diabetes Prevention Project and other related trials in individuals at high risk for the development of diabetes. Whatever changes the person makes must be sustained to be beneficial. The clinician should assess the current diet with a good nutritional history, which may involve a verbal 24- or 72-hour diet recall. Alternatively, the patient may keep a written 3- to 7-day food diary. Assessing meal patterns is important because many people skip breakfast and eat lunch erratically. Attention should be paid to how often the person eats out, especially fast food. Many patients can identify key foods that are a problem for their weight loss efforts. Small, gradual changes may be more successful than drastic ones.

25. Should patients be encouraged to attend a commercial weight loss program?

Current guidelines suggest the most effective behavioral treatment for obesity is a high-intensity, comprehensive weight loss intervention provided in individual or group sessions by a trained interventionist with principal components of a moderately reduced calorie diet, increased physical activity, and behavioral support to facilitate adherence. Most people know what they should eat. The problem is that they either do not pay attention to what they eat or do not find a "healthy diet" palatable. The use of commercial programs, such as Weight Watchers or TOPS (Taking Off Pounds Sensibly), can provide reasonable nutritional counseling along with social support that often cannot be provided in the context of a busy office practice. Many patients are surprised at the cost of these programs, which may be a deterrent to their continued use. The scientific literature supports the notion that for many people, commercial weight loss programs are a reasonable option.

26. Are meal replacements useful in a weight loss program?

For some people, it is difficult to control calories through self-selected meals. Time may not be available for food preparation, and convenience may override health concerns. For such people, meal replacements, which are reduced-calorie, nutritionally complete meals, are a reasonable option with scientifically proven effectiveness if used as a long-term strategy. In fact, this approach was used in the NIH-funded Look Ahead Trial, and participants who were in the highest quartile of meal replacement use were four times more likely to meet their weight loss goals.

27. What are low- and very low-caloric diets? When should their use be considered?

A very low-caloric diet (VLCD) is a nutritionally complete diet of 800 kcal/day that produces rapid weight loss. A low-caloric diet (LCD) contains between 800 and 1000 kcal/day. Commercially available products typically consist of liquid meals that have been supplemented with essential amino acids, essential fatty acids, vitamins, and micronutrients taken four to five times per day. Supplementing the commercial product with fruits and vegetables converts a VLCD to an LCD and may make the diet more tolerable to patients. Recent data suggests that VLCDs and LCDs may produce a degree of weight loss that is better than traditional dietary approaches and closer to what is seen with bariatric surgery. These diets may also be useful for the patient who needs short-term weight loss for a diagnostic or surgical procedure. Gallstone formation is a recognized complication of these diets.

28. What is alternate-day fasting? What is time-restricted eating?

A multitude of dietary strategies exist that may lead to weight loss success for some individuals. Two strategies that have recently become more popular and are starting to have a stronger evidence base are alternate-day fasting and time-restricted eating. There are several forms of alternate-day fasting, but probably the most used version involves “modified” fasting where 500 kcal are an allowable intake on fasting days. Time-restricted eating is a form of intermittent fasting where eating is reserved for a certain period of the day only, such as from 8 AM until 4 PM. The remainder of the day is a fasting period, and this schedule is repeated daily.

29. What medications are available to treat obesity?

- Phentermine (Adipex-P, Fastin, Ionamin, Lomaira)
- Orlistat (Xenical, Alli)
- Phentermine plus topiramate ER (Qsymia)
- Naltrexone plus bupropion SR (Contrave)
- Liraglutide (Saxenda)
- Semaglutide (Wegovy)
- Tirzepatide (Zepbound)

30. Discuss the role of exercise in a weight loss program.

Although exercise does not produce much added weight loss over diet alone, it appears to be extremely important in maintaining the reduced state. The National Weight Control Registry is a group of 3000 people who were identified because they successfully lost 30 lb. and maintained this weight loss for at least 1 year. They self-report 2000 kcal/week of planned physical activity (60–80 min/day on most days of the week). A discussion of physical activity should begin with a physical activity history. Ask about the frequency of engaging in planned physical activity and any physical limitations that make it difficult to exercise. Then ask about hours per day of sedentary behavior including television viewing and computer time. Finally, discuss activities of daily living, including work-related activities. Assess the individual’s readiness to change his or her physical activity.

31. How much physical activity is necessary to prevent weight gain as opposed to maintaining a reduced weight?

In 2008, the federal government published physical activity guidelines for Americans. These guidelines suggest that all adults should do 150 minutes a week of moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity. In addition, they advise muscle-strengthening activities that involve all major muscle groups be performed on 2 or more days per week. This level of activity is designed to prevent weight gain. It appears that 60–90 minutes per day of moderate physical activity may be needed for maintenance of weight loss. People in the National Weight Control Registry who use physical activity to maintain a reduced obese state average 12,000 steps/day.

The specifics on when or how to exercise are currently being investigated. For now, the recommendation to exercise when convenient for the patient and using the modality most enjoyable by the patient is recommended. Early literature suggests that for specific patient populations (i.e., patients with diabetes) exercising after a meal may be of glycemic benefit, but no differences in weight loss have been found. Similarly, the intensity at which the patient exercises (assuming similar energy expenditure) has not been associated with differences in weight outcomes. However, resistance and balance training have been implicated in several other health benefits, including reduced falls in the elderly.

32. What are the main types of bariatric/metabolic surgery?

The main types of bariatric surgery are Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch, and gastric banding. Both Roux-en-Y and sleeve gastrectomy function by either bypass or resection of much of the stomach. Both result in increased gastric emptying and increased satiety with smaller amounts of intake. Biliopancreatic diversion is a complex procedure involving a sleeve gastrectomy (removal of most of the stomach) and anastomosis between the proximal duodenum and intestine. Biliopancreatic diversion is designed to also cause a degree of malabsorption and is therefore associated with a higher incidence of complications. Gastric banding is the implantation of a device that constricts the stomach and can be adjusted to fit the patient's needs.

33. How successful and what are the major complications of bariatric/metabolic surgeries?

As in most treatments of obesity, the weight loss benefit from surgery is variable amongst patients. Weight loss for Roux-en-Y has been reported as high as 35% after 1 year, where gastric banding typically produces more modest weight loss of 12–16%. Biliopancreatic diversion has been shown to have the most robust weight loss, though typically at the cost of higher postoperative complications.

It should be noted that the benefit of substantial weight loss for patients with obesity often outweighs the risk of bariatric surgery, although each patient should be examined individually for risk. Short-term complications are uncommon and similar to other major abdominal surgeries (wound healing issues, anesthesia complications, deep vein thrombosis or pulmonary embolism, and infection). All these risks are higher in patients with obesity versus lean counterparts. Long-term complications of bariatric surgery include intestinal obstruction, ulcers, hernias, cholelithiasis, hypoglycemia, and mineral and vitamin deficiencies (particularly iron, vitamin D, and vitamin B_{12}).

34. What major medical organizations and societies support the use of antiobesity pharmacotherapy for the treatment of obesity?

In recent years numerous medical organizations and societies have published guidelines that support the use of antiobesity medications. Some of the organizations include the Endocrine Society, American Association of Clinical Endocrinology, American Heart Association, American College of Cardiology, The Obesity Society, and Veterans Health Administration.

35. When is antiobesity pharmacotherapy medically indicated?

Antiobesity pharmacotherapy (see Table 12.1) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition.

36. What barriers exist to the more widespread use of antiobesity medications?

Well-recognized barriers to the use of antiobesity pharmacotherapy include the perception by some that obesity is not a disease that warrants pharmacologic therapy, lack of provider training regarding the proper use of the medications, and general absence of insurance coverage resulting in high out-of-pocket cost.

TABLE 12.1 FDA-Approved Weight Loss Medications

	PHENTERMINE	ORLISTAT	PHENTERMINE + TOPIRAMATE ER	NALTREXONE + BUPROPION SR	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
Brand name	N/A	Xenical (Rx) Alli (OTC)	Qsymia	Contrave	Saxenda	Wegovy	Zepbound
Mechanism	Appetite suppressant; sympathomimetic	Gastrointestinal lipase inhibitor	Appetite suppressant; sympathomimetic. Topiramate mechanism unknown	Appetite suppressant; selective serotonin 2C receptor agonist	GLP1 agonist (enhances satiety, slows gastric emptying)	GLP1 agonist (enhances satiety, slows gastric emptying)	GLP1 and GIP agonist (enhances satiety, slows gastric emptying)
Dose/Route	8–37.5mg PO daily (in AM)	60–120mg PO before meals	3.75/23–15/92mg PO daily	8/90–32/360mg PO daily	0.6–3.0mg SQ weekly	0.25–2.4mg SQ weekly	2.5–15mg SQ weekly
Side Effects	Tachycardia, hypertension, dry mouth, headache, tremor	Diarrhea, steatorrhea, fat soluble vitamin malabsorption, liver toxicity	Tachycardia, hypertension, insomnia, agitation, dry mouth, headache, tremor, suicidal ideations, glaucoma, sleep disorders, metabolic acidosis, renal injury	Tachycardia, hypertension, nausea, constipation, headache, suicidal ideations	Nausea, vomiting, diarrhea, constipation, dyspepsia, pancreatitis	Nausea, vomiting, diarrhea, constipation, dyspepsia, pancreatitis	Nausea, vomiting, diarrhea, constipation, dyspepsia, pancreatitis
Percent body weight loss versus placebo (maximum dose)	5%	4–5%	10%	5%	7%	17%	21%
Contraindications	Uncontrolled hypertension, coronary artery disease, congestive heart failure	Malabsorption, chronic diarrhea, cholestasis, calcium oxalate nephrolithiasis	Recent cardiovascular event, ESRD, hepatic impairment, cholelithiasis, nephrolithiasis, uncontrolled depression, MAOIs, carbonic anhydrase inhibitors	Uncontrolled hypertension, seizures, eating disorders, opiate use, MAOIs, alcohol use	Personal or family history of medullary thyroid cancer, severe gastrointestinal disease, gastroparesis, history of pancreatitis	Personal or family history of medullary thyroid cancer, severe gastrointestinal disease, gastroparesis, history of pancreatitis	Personal or family history of medullary thyroid cancer, severe gastrointestinal disease, gastroparesis, history of pancreatitis
Relative cost ($–$$$$)	$	Alli $$ (OTC) Xenical $$$ (Rx)	$$	$$$	$$$$	$$$$	$$$$

37. Are phentermine and amphetamine related?

Yes, phentermine is chemically related to amphetamine and works predominantly on the neurotransmitter norepinephrine to reduce appetite. The addictive effects of amphetamine are thought to be due to its actions on the neurotransmitter dopamine. Phentermine has substantially fewer dopaminergic effects than amphetamine and thus has minimal potential for addiction.

38. Is phentermine effective? What is the usual dose?

Phentermine, an appetite suppressant, is the most prescribed antiobesity pharmacotherapy in the United States. Compared with placebo, phentermine produces roughly a 5% weight loss in 50% to 60% of those who take it. The dose used ranges from 15 to 37.5 mg once daily or 8 mg that can be taken up to three times daily before meals.

Clinically, some patients respond to phentermine and others do not. Therefore, it may be helpful to start a patient on a trial of phentermine and, if >5% weight loss is not met by 3–6 months, consider an alternative agent.

39. Discuss the side effects of phentermine.

Phentermine is a central stimulant and can cause hypertension, tachycardia, nervousness, headache, difficulty sleeping, and tremor in some people. It should not be used in people with uncontrolled hypertension. Blood pressure should be monitored closely after initiation of this medicine. There is no evidence that, when used alone (in contrast to the combination of phentermine with fenfluramine), it is associated with cardiac valvular or pulmonary vascular toxicity. Phentermine is only approved by the Food and Drug Administration (FDA) for 3-month use. However, it has been widely prescribed longer than any other weight loss agent, and there has been no evidence of serious long-term side effects.

40. How does orlistat work? What is the usual dose? What are the side effects?

Orlistat is a pancreatic lipase inhibitor. At the prescription strength of 120 mg three times a day with meals (trade name Xenical), it reduces the absorption of dietary fat by roughly 30% by inhibiting the enzyme responsible for fat digestion. The average weight loss seen is about 5% to 8%. This medication may be preferred in people with mood disorders, heart disease, or poorly controlled hypertension. A 60-mg form (trade name Alli) is approved by the FDA and available over the counter. This strength is less effective than the prescription strength, giving roughly a 2% to 4% weight loss.

The main side effects are due to the malabsorption of fat. Patients who eat a high-fat meal experience greasy stools and may even have problems with incontinence of stool. If the patient chooses to skip the medication, he or she can eat a high-fat meal without side effects and without the benefit that the medication would otherwise provide. The FDA has approved orlistat for long-term use, and there is no specific mention in the package insert of when it should be stopped. Because of the potential to cause fat-soluble vitamin deficiencies, patients should be instructed to take multiple vitamins daily. Orlistat should be used with caution in those taking coumadin (warfarin) and is contraindicated in those on cyclosporine.

41. Discuss the use of phentermine plus topiramate extended release in obesity treatment.

Topiramate is indicated for the treatment of seizure disorder and migraine. In clinical trials, individuals taking phentermine plus topiramate had a mean weight loss of 8–10%. The recommended dose is phentermine 7.5 mg plus topiramate extended release 46 mg. The higher dosage of phentermine 15 mg plus topiramate 92 mg can also be prescribed. The combination medication (trade name Qsymia) cannot be used during pregnancy because data have shown that fetuses exposed to topiramate during the first trimester are at increased risk of oral clefts (cleft lip with or without cleft palate). Females of reproductive age should have a negative pregnancy test before starting the medication, should use effective contraception, and should have pregnancy tests every month while on the medication. Additionally, the medication cannot be used in patients with glaucoma or hyperthyroidism.

42. Discuss the use of naltrexone plus bupropion sustained release in obesity treatment.

Bupropion is a dopamine and norepinephrine reuptake inhibitor that stimulates POMC neurons. When combined with naltrexone (an opioid antagonist), bupropion enhances efficacy by releasing feedback inhibition of POMC neurons that naltrexone potentiates. The combination of the two medications was FDA-approved in 2014 for chronic weight management (trade name Contrave). The average weight loss with the combined medication was approximately 5% in clinical trials. Common side effects include nausea, constipation, headache, and dizziness. The medication should not be used in patients with uncontrolled hypertension, seizure disorders, anorexia or bulimia, those with drug or alcohol withdrawal, and patients concurrently taking opioids or monoamine oxidase inhibitors.

43. Discuss the use of glucagon-like peptide-1 (GLP-1) receptor agonists in obesity treatment.

Liraglutide and semaglutide are glucagon-like peptide-1 (GLP-1) receptor agonists that were both initially approved at lower doses for diabetes (trade names Victoza and Ozempic). Studies indicated that more weight loss was achieved with the medications when given at higher doses. In 2014, the FDA approved liraglutide specifically for the chronic management of obesity at a dose of 3.0 mg (trade name Saxenda), and in 2021 higher-dose semaglutide 2.4 mg was approved (trade name Wegovy). The average weight loss in the major clinical trial of liraglutide was 5.8 kg. Semaglutide resulted in a higher average weight loss of 15.3 kg in a trial for this medication for weight loss in participants without diabetes. Common side effects are primarily gastrointestinal (nausea, vomiting, diarrhea, or constipation), and there is concern about an increased risk of pancreatitis with these medications. People with a personal or family history of medullary thyroid cancer and/or multiple endocrine neoplasia type 2 should avoid these medications. There is clinical trial evidence that liraglutide and semaglutide delay the progression from prediabetes to diabetes.

44. Discuss the use of tirzepatide in obesity treatment.

The most recently approved medication for obesity treatment is tirzepatide (Zepbound), which was FDA approved in November 2023. Tirzepatide is a dual agonist, acting on both the GLP-1 receptor and the glucose dependent insulinotropic polypeptide (GIP) (previously gastric inhibitory polypeptide [GIP]) receptor. Tirzepatide (brand name Mounjaro) has been used since 2022 for the treatment of type 2 diabetes and is considered to be a stronger medication than semaglutide when used at higher doses. In studies specifically in people with obesity without type 2 diabetes, tirzepatide results in an average of 19.5% weight reduction over 72 weeks.

45. What evidence supports GLP-1 agonist use in patients with obesity to prevent cardiovascular events?

In the SELECT trial, semaglutide 2.4 mg weekly was found to be superior to placebo in the prevention of death from cardiovascular causes, nonfatal MI, and nonfatal stroke in patients without diabetes but with obesity and preexisting heart disease. In March 2024, the FDA approved an expanded indication for semaglutide to reduce the risk of cardiovascular death, heart attack, and stroke in adults with overweight or obesity and established cardiovascular disease, making it the first weight loss medication approved for this specific purpose. A similar study is ongoing with tirzepatide (SURMOUNT-MMO) with the results expected in 2027 or 2028.

46. What are some new and upcoming therapies for the treatment of obesity?

The world of antiobesity pharmacotherapy is expanding at a rapid pace. A recent publication of a triple agonist (GLP-1/GIP/Glucagon) called retatrutide resulted in an average of 23% body weight reduction in participants with overweight or obesity on the maximum dose. This trial marked phase 2 completion of this medication investigation, and FDA approval is likely several years down the road. Similarly, a combination medication of GLP-1 agonist and amylin analog (semaglutide/cagrilintide) has been shown to result in a 16% body weight loss in participants with type 2 diabetes. Orforglipron (an oral nonpeptide GLP-1 receptor agonist) and oral semaglutide are also under investigation and result in a 12–15% weight reduction.

47. How long will antiobesity pharmacotherapy need to be taken?

Medications used to promote weight loss will work only as long as they are taken, and most weight loss is achieved in the first 3–9 months of therapy. If a patient loses weight while taking a medication and then stops using it, he or she is likely to regain the lost weight. If a physician and a patient decide to try antiobesity pharmacotherapy, it should be taken for a minimum of 3 months to determine whether the patient will experience a weight loss benefit. Then some form of chronic use should be considered, given the available information about the risks and potential benefits of the medication. There are also data supporting the intermittent use of antiobesity pharmacotherapy.

KEY POINTS

- Overweight and obesity are defined as degrees of excess weight associated with increases in morbidity and mortality. Obesity is associated with diabetes, hypertension, hyperlipidemia, coronary artery disease, degenerative arthritis, gallbladder disease, and cancer of the endometrium, breast, prostate, and colon.
- Treatment options for patients with overweight and obesity include diet, exercise, pharmacotherapy, surgery, and combinations of these modalities.
- Evidence supports that sustained 5% to 10% weight loss is adequate for measurable health benefits.
- Antiobesity pharmacotherapy and/or bariatric surgery are indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with BMI of 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition or 30 kg/m^2 or greater.
- FDA approved medications for the treatment of obesity include phentermine, orlistat, phentermine plus topiramate ER, naltrexone plus bupropion SR, liraglutide, semaglutide, and tirzepatide.

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CHAPTER 13

Osteoporosis and Other Metabolic Bone Diseases

Michael T. McDermott

1. What is osteoporosis?

Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing to the development of fragility fractures. The diagnosis of osteoporosis is established by the presence of a fragility fracture, by low bone mass on bone mineral density (BMD) testing, or with the FRAX Risk Assessment tool. Bone strength is determined by both *bone mass* and *bone quality*.

2. What are fragility fractures?

Fragility fractures are those that occur spontaneously or following minimal trauma, defined as falling from a standing height or less. Vertebral, hip, and distal radius (Colles') fractures are the most characteristic, but osteoporosis predisposes to all types of fractures. Nearly 40% of women and 13% of men develop one or more osteoporotic fractures during their lifetime. Osteoporosis accounts for approximately 1.5 million fractures in the United States each year.

3. What are the complications of osteoporotic fragility fractures?

Vertebral fractures cause height loss, anterior kyphosis (dowager's hump), reduced pulmonary function (FVC decreases 9% for each vertebral fracture), and an increased mortality rate. Only one-third of all vertebral fractures are painful while two-thirds are asymptomatic. Hip fractures cause permanent disability in approximately 50% of people and a 20% excess mortality rate compared to the age-matched nonfracture population.

4. What factors contribute most to the risk of developing an osteoporotic fracture?

- Low Bone Mineral Density (BMD) (2x increased risk for every one standard deviation [T-score] BMD decrease)
- Age (2x increased risk for every decade of age above 60 years)
- Previous fragility fracture (5x increased risk for a previous fracture)
- Corticosteroid use
- Frequent falls

5. How is the diagnosis of osteoporosis made?

Osteoporosis is diagnosed by any of three criteria: fragility fracture, low BMD, high FRAX risk score.

FRAGILITY FRACTURE CRITERIA

- A fragility fracture establishes a diagnosis of osteoporosis, regardless of the BMD T-score.

BONE DENSITOMETRY CRITERIA

- BMD T-score ≤-2.5 at any site indicates osteoporosis in people >age 50 years; diagnostic T-score ranges are as follows:

T-score ≥ −1	Normal
T-score −1 to −2.5	Osteopenia
T-score ≤ −2.5	Osteoporosis

- In premenopausal women or men <age 50 years, a BMD **Z**-score ≤-2.0 at the lowest skeletal site indicates low BMD for age.

FRAX RISK ASSESSMENT CRITERIA

- A FRAX 10 Year Risk Score: ≥3% for hip fracture or ≥20% for major osteoporosis fractures also diagnoses osteoporosis.

6. How do you determine if a patient has had a previous vertebral fracture?

Back pain or tenderness are clues but may be absent, since two-thirds of vertebral fractures are asymptomatic. Height loss of ≥2 inches or dorsal kyphosis are highly suggestive clinical findings. Vertebral imagining with lateral spine films or DXA vertebral fracture assessment (VFA) are the most accurate ways to detect existing vertebral fractures.

7. How is BMD currently measured?

Dual-energy x-ray absorptiometry (DXA) is the most accurate and widely used method in current practice. Radiation exposure is minimal with only 1–3 uSv/site compared with 50–100 uSv for one chest radiograph. BMD can also be measured by computed tomography (CT) (50 uSv) and ultrasound (US) (no radiation). Central densitometry measurements (spine and hip) are the best predictors of fracture risk and have the best precision for longitudinal monitoring. Peripheral densitometry measurements (heel, radius, hands) are more widely available and less expensive but are less accurate. Bone densitometry testing is covered in Chapter 14.

8. What are the currently accepted indications for BMD measurement?

- Age ≥65 years (women); age ≥70 years (men).
- Estrogen deficiency plus one risk factor for osteoporosis.
- Vertebral deformity, fracture, or osteopenia by x-ray.
- Primary hyperparathyroidism.
- Glucocorticoid therapy ≥5 mg/day of prednisone for ≥3 months.
- Monitoring the response to an FDA-approved osteoporosis medication.

9. How do you read a bone densitometry report?

T-score: Number of SD the person deviates from the mean BMD for young normal subjects (peak bone mass). T-score is the best predictor of fracture risk.

Z-score: Number of SD the person deviates from the mean BMD for age-matched normal subjects. Z-score indicates if the BMD is appropriate for age. A low Z score is predictive of an underlying secondary cause other than age or menopause.

Absolute BMD: Actual BMD in gm/cm^2. This value should be used to calculate changes in BMD during longitudinal follow-up.

10. What estimates of bone loss and fracture risk can be made from a person's BMD measurement by DXA?

T-score	*% Bone Loss**	*Fracture Risk Increase*
–1	12%	2-Fold
–2	24%	4-Fold
–3	36%	8-Fold
–4	48%	16-Fold

*Note: one must lose 30% of BMD to see osteopenia on a routine radiograph; this degree of loss suggests a T-score of –2.5.

11. How do you use the FRAX Risk Assessment tool?

The Fracture Risk Assessment (FRAX) tool (www.shef.ac.uk/FRAX/) is a free computer-based program developed by the World Health Organization (WHO). It uses clinical risk factors with or without femoral neck BMD to provide a 10-year absolute risk estimate for developing a hip or another major osteoporotic fracture. It is recommended for making treatment decisions in drug-naïve people over age 40 with *osteopenia* on BMD testing and without fragility fractures. Treatment is advised for those who have a 10-year risk ≥3% for hip fracture or ≥20% for major osteoporosis fractures.

12. What is a trabecular bone score and how is it used?

Trabecular bone score (TBS) is a newer technique developed to evaluate bone quality. TBS uses data from existing DXA lumbar spine images to produce a gray-level textural index that correlates well with fracture risk in postmenopausal women and in men age ≥50 years. It can be used in conjunction with DXA to assist with decisions about initiation of osteoporosis therapy. The TBS can also be entered into the FRAX Risk Assessment tool. It should not be used alone and is not validated as a tool for monitoring therapy. TBS is particularly useful in disorders for which DXA alone significantly underestimates fracture risk, such as glucocorticoid induced osteoporosis and diabetes mellitus.

13. What are the major risk factors for the development of osteoporosis?

NonModifiable	***Modifiable***
Advanced age	Low calcium intake
Race (Caucasian, Asian)	Low vitamin D intake
Female gender	Estrogen deficiency
Early menopause	Sedentary lifestyle
Slender build (<127 lb)	Cigarette smoking
Positive family history (hip fx)	Alcohol excess (>2 drinks/day)
	Caffeine excess (>2 servings/day)

Note: Mental disorders, use of antipsychotic medications and hyponatremia have all been reported to increase the fracture risk.

14. What other conditions must be considered as causes of low BMD?

Osteomalacia
Osteogenesis Imperfecta
Ehlers-Danlos syndrome
Hyperparathyroidism
Hyperthyroidism
Hyperprolactinemia
Alcoholism
Hypogonadism
Cushing's Syndrome
Eating/Exercise Disorders
Celiac Disease
Inflammatory Bowel Disease
Gastrectomy/bowel bypass surgery
Primary Biliary Cirrhosis
Multiple Myeloma
Rheumatoid Arthritis/SLE
Ankylosing spondylitis
Chronic Kidney Disease
Renal Tubular Acidosis
Idiopathic Hypercalciuria
Systemic Mastocytosis
High Risk Medications[*]

[*] Glucocorticoids, excess thyroid hormone, anticonvulsants, heparin, lithium, SSRIs, aromatase inhibitors, premenopausal tamoxifen, leuprolide, cyclosporine. Probable/Possible: Thiazolidinediones, proton pump inhibitors, excess vitamin A.

15. Outline a cost-effective evaluation to rule out other causes of low bone mass.

Calcium, albumin, phosphorous, creatinine, CO_2
Alkaline phosphatase
25 OH vitamin D
Testosterone (Men)
Thyroid-stimulating hormone (TSH) (if hyperthyroidism suspected clinically)
Celiac disease testing (Caucasians with symptoms or low 25 OH Vitamin D level)
Urine (24 hour) calcium, sodium, creatinine
SPEP (if over age 50 and abnormal CBC or high protein gap)

Note: Approximately one-third of women and two-thirds of men will have an abnormality detected. This cost-effective evaluation is recommended in all osteoporosis patients. A low Z score suggests that an underlying secondary cause is even more likely to be present.

16. What are the most significant risk factors for frequent falls?

Frailty
Use of sedatives
Visual impairment
Cognitive impairment
Lower extremity disability
Obstacles to ambulation in the home

Note: The most predictive factor for a future fall is a previous fall within the past 6 months. Almost all hip fractures occur due to falls. Falls have been shown to predict fractures independently of the FRAX risk score.

17. How does osteoporosis differ in men?

Approximately 1–2 million men in the United States have osteoporosis. The diagnostic criteria are the same in men as in women (fragility fracture, T-score ≤-2.5, FRAX risk scores). Nearly two-thirds of osteoporotic men have an identifiable secondary cause of bone loss, most often alcohol abuse, glucocorticoid use, and hypogonadism, including GnRH analog use for prostate cancer. Treatment is the same in men as in women, although testosterone replacement in hypogonadal men is an effective adjunctive strategy.

18. How do glucocorticoids cause osteoporosis?

Glucocorticoids adversely affect both phases of bone remodeling leading to rapid bone loss. Bone formation is inhibited by accelerated osteoblast apoptosis and reduced new osteoblast development. Bone resorption is stimulated by decreased sex steroid levels and reduced production of osteoprotegerin, an endogenous bone resorption inhibitor. Osteocytes also undergo accelerated apoptosis.

Note: People on glucocorticoids fracture at higher/better BMD values (T-scores) than do people with other types of osteoporosis.

19. Define the fracture risk categories for glucocorticoid induced osteoporosis?

Adults ≥40 Years of Age

Low Risk
FRAX: MOF <10%, Hip Fracture <1%
BMD: T-score >-1.0
Moderate Risk
FRAX: MOF 10–20%, Hip Fracture 1–3%
BMD: T-score -1.0 to -2.4
High Risk
FRAX: MOF 20–30%, Hip Fracture 3–4.5%
BMD: T-score ≤-2.5
Very High Risk
FRAX: MOF >30%, Hip Fracture >4.5%
BMD: T-score ≤-3.5, OR
Prior osteoporosis fracture, OR
GC dose ≥30 mg/day for >30 days or cumulative dose ≥5 g/year

Adults ≤40 Years of Age

Low Risk
None of the above risk factors other than CG treatment
Moderate Risk
Ongoing CG treatment ≥7.5 mg/day for ≥6 months and BMD T-score <-3.0 OR significant bone loss compared to prior BMD (>least significant change)
High Risk
Prior osteoporosis fracture, OR
GC dose ≥30 mg/day for >30 days or cumulative dose ≥5 g/year
Very High Risk
Prior osteoporosis fracture, OR
GC dose ≥30 mg/day for >30 days or cumulative dose ≥5 g/year
FRAX CG Adjustment: If GC dose ≥7.5 mg/d, multiply MOF risk x 1.15 and Hip Fx risk x 1.2

*MOF: Major osteoporosis fracture.

20. How should people on glucocorticoids (GC) be assessed and monitored?

2022 recommendations of the American College of Rheumatology:

Adults (≥18 years old) starting or continuing GC therapy (prednisone dose ≥2.5 mg/day or equivalent) for ≥3 months should have an initial clinical fracture risk assessment (fracture history, BMD, FRAX [age >40 only], and lateral spine radiographs or VFA).

Adults on chronic CG therapy (≥2.5 mg/day but <7.5 mg/day) at low fracture risk and not recommended to start osteoporosis (OP) medications, or moderate fracture risk who chose not to start OP medications, should have fracture risk repeated every 1–2 years.

Adults on chronic CG therapy (≥2.5 mg/day) at moderate, high, or very high fracture risk and continuing OP medications ≥1 year should have fracture risk repeated every 1–2 years.

21. Discuss the causes and treatment of osteogenesis imperfecta.

Osteogenesis Imperfecta (OI) results from defective osteoblast function due most commonly to mutations in genes that encode the alpha-1 and alpha-2 chains of type I collagen (*COL1A1* and *COL1A2*). Autosomal recessive OI is caused by mutations in genes that encode proteins involved in type I collagen posttranslational modification (*FKBP10*, *CRTAP*, *LEPRE1*, *PPIB*) or other regulators of bone formation and homeostasis (*SERPINH1*, *SERPINF1*, *SP7/OSX,* and *IFITM5*). OI varies in clinical features and severity. OI is best diagnosed with genetic testing.

Therapy goals are to prevent fractures, deformities, pain, and functional impairment. Data on the risks and benefits of pharmacologic therapy are sparce. Bisphosphonates are used for most forms of OI, but not type VI, in which bone mineralization is defective and bisphosphonates may be harmful. Anabolic therapy has also been used, but its effects are dependent on the underlying mutation. People with OI are best managed in centers where there is experience treating this condition.

22. What is hypophosphatasia?

Hypophosphatasia results from inherited inactivating mutations of the gene that encodes the tissue nonspecific alkaline phosphatase isoenzyme (ALPL). The severity of the enzyme defect determines the clinical features, which vary from fetal demise to disabling pediatric forms to milder adult forms manifested by rickets or osteomalacia, dental abnormalities, multiple fractures or just osteoporosis. Low serum alkaline phosphatase, elevated vitamin B_6 or pyridoxal phosphate, and high urine phosphoethanolamine levels suggest the diagnosis, which can be confirmed with genetic testing. Recently, enzyme replacement, asfotase alpha, has become available for treatment of the more severe cases.

23. Define osteopetrosis.

Osteopetrosis (marble bone disease) results from defective osteoclast function. Mutations have been identified in the following genes: *TCIRG1* (proton pump), *CLCN7* (chloride channel), *CAII* (carbonic anhydrase II), and *gl/gl* (unknown function). Each of these abnormalities leads to the inability of osteoclasts to create an acidic environment in the resorption pit under its ruffled border, which is needed for the dissociation of calcium hydroxyapatite from the bone matrix. The impaired bone resorption produces dense, chalky, fragile bones and bone marrow replacement. Skeletal x-rays show generalized osteosclerosis. The diagnosis is made by genetic testing. Bone marrow transplantation to provide normal osteoclasts may be needed in severe cases while high-dose calcitriol to stimulate osteoclasts can be effective in the milder forms.

KEY POINTS

- The major risk factors for fragility fractures are low bone mass, advancing age, previous fragility fractures, corticosteroid use, and the propensity to fall.
- Disorders causing secondary bone loss are present in approximately one-third of women and two-thirds of men who have osteoporosis.
- Osteoporosis patients should have a complete history and physical examination and key, cost-effective laboratory tests to identify any underlying responsible disorders.
- High doses and prolonged use of glucocorticoids produce greater risk, but all doses of oral glucocorticoids and even inhaled steroids increase the risk of osteoporotic fractures.
- Glucocorticoid induced-osteoporosis results from a combination of suppressed bone formation and enhanced bone resorption accounting for the rapid bone loss often seen in glucocorticoid treated patients.

TOP SECRETS

If a person has a fragility fracture, this makes the diagnosis of osteoporosis regardless of the bone mineral density or FRAX risk score.

Each vertebral fracture reduces pulmonary forced vital capacity (FVC) by about 9%.

The FRAX tool is designed to assess fracture risk for therapeutic decision-making only in osteoporosis drug–naïve people who have osteopenia on bone mineral density testing.

Glucocorticoids cause rapid bone loss because they adversely affect both major areas of bone remodeling, simultaneously inhibiting bone formation and promoting bone resorption.

WEBSITES

The National Osteoporosis Foundation: www.nof.org
NIH Osteoporosis and Related Bone Diseases - National Resource Center: www.osteo.org
American Society for Bone and Mineral Research: www.asbmr.org
Bones and Osteoporosis: www.bones-and-osteoporosis.com
International Society for Clinical Densitometry: www.iscd.org

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Measurement of Bone Mass

Christine M. Swanson

1. What is bone mineral density (BMD)?

BMD usually refers to areal bone mineral density (aBMD), a two-dimensional (2D) approximation of bone mass, estimated as grams (g) per square centimeter (cm^2). aBMD is dependent on bone size (i.e., smaller bones appear less dense). It is obtained from a Dual-Energy X-ray Absorptiometry (DXA) scan and derived by dividing the Bone Mineral Content (BMC) in g by the bone area in cm^2. BMC is a measure of the mineral (primarily calcium) found in bone. The amount of x-ray energy absorbed by calcium reflects the BMC. Although less commonly used clinically, volumetric BMD (vBMD) can be measured at the lumbar spine (L-spine) and hip with 3D quantitative computed tomography (QCT). vBMD is expressed in g/cm^3 and is not dependent on bone size. BMD-fracture associations refer to aBMD, and BMD in this chapter will refer to aBMD unless otherwise noted.

2. What techniques are used to measure bone mass and what is the preferred method?

The most commonly used and accepted technique for measuring bone mass is central DXA. Central DXA is preferred because it is noninvasive, low cost, has relatively minimal radiation exposure (1–10 **μ**Sv) with short scanning times, good precision, and extensive data supporting its relationship to fracture risk and response to treatment. Central DXA estimates aBMD at the L-spine, hip (including femoral neck), and sometimes the 33% radius of the forearm. The most commonly used DXA machines are made by Hologic, General Electric Healthcare (GE Lunar), and Norland. Portable peripheral DXA (pDXA) can assess BMD at peripheral sites (e.g., radius). DXA-generated BMD from central sites have superior fracture risk prediction, but pDXA can be used to assess fracture risk. pDXA should not be used to diagnose osteoporosis or to monitor BMD. “DXA” in this chapter will refer to central DXA, unless otherwise noted. Quantitative ultrasound (QUS) uses the velocity of ultrasound passing through bone to assess calcaneal BMD. QUS is often discordant from central DXA. Central DXA is preferred, but if unavailable, QUS can be used for fracture risk assessment and initiating treatment but not for monitoring. QCT assesses vBMD but requires more time and radiation exposure than DXA. Some software applications can provide DXA-equivalent aBMD values from QCT at the proximal femur. Peripheral QCT (pQCT) devices assess vBMD at the tibia and forearm. High-resolution peripheral QCT (HR-pQCT) measures vBMD at the distal radius and distal tibia, can differentiate cortical and trabecular bone compartments, and is primarily used for research. Assessing L1 attenuation on a previously performed body CT (often called “Opportunistic bone mineral density” or “Opportunistic CT”) by measuring the Hounsfield units (HU) at L1 has been shown to correlate with DXA-derived L-spine T-scores and vertebral fracture risk. L1 attenuation ≤ 90 HU is considered low. Opportunistic CT may be used when other anatomical sites are not available (e.g., presence of hardware) or as a screening tool to help assess when a DXA should be obtained. Routine x-rays are not sensitive enough to assess BMD because demineralization is not visually apparent on x-ray until ≥40% of bone density is lost.

3. Why is BMD important?

BMD is one of the most important determinants of bone strength and fracture risk. Fracture risk increases as BMD decreases and fracture risk doubles for every standard deviation decrease below the young adult mean (i.e., fracture risk doubles for every 1.0 decrease in the T-score). Hip BMD predicts hip fracture risk, and BMD at the hip and L-spine predict vertebral fracture risk. BMD from DXA is used to assess fracture risk, to diagnose low bone mass/osteoporosis, and to monitor changes in bone density over time while on or off osteoporosis medications. Serial DXA exams

TABLE 14.1 Indications for Bone Mineral Density (BMD) Testing

Women ≥65 years old and men ≥70 years old
Postmenopausal women and men who are ≥50 years old with an adult fracture or risk factor for osteoporosis/fracture. Risk factors include (but are not limited to): • Low body weight (<127lbs) or low BMI (<20 kg/m^2) • Use of bone-harming medications (e.g., glucocorticoids, antiepileptic drugs, aromatase inhibitors, etc.) • Disease or condition associated with bone loss (e.g., hypogonadism, hyperparathyroidism, premature menopause, etc.) • Rheumatoid arthritis • Family history of osteoporosis or hip fracture • Current tobacco use • Excessive alcohol use
Individuals initiating or taking systemic glucocorticoid therapy for ≥ 3 months
Anyone with "low bone mass" on x-ray

must be performed on the same machine at the same facility for accurate BMD trend analysis over time (*see Question #14*).

4. Who should get a bone density screening test?

It is recommended that a screening DXA be performed in certain groups (Table 14.1). Baseline and serial bone density exams should be considered in those who are initiating or have been on bone-harming medications (e.g., glucocorticoids, aromatase inhibitors, antiepileptic medications, etc.), those initiating or already on pharmacological therapy for osteoporosis, and/or those at risk for bone loss. Insurance coverage of DXA in certain groups may vary (e.g., screening DXA in men may not be covered).

5. What anatomical sites are routinely measured?

A minimum of two anatomical sites are recommended for BMD assessment. Central DXA typically measures BMD at the L-spine (L1–4) in the anterior-posterior (AP), not lateral, orientation, and at one or both proximal femurs. The two most important regions of interest (ROI) at the proximal femur are the femoral neck and the total hip (which includes the femoral neck). Other proximal femur sites reported (e.g., Ward's triangle, trochanteric) are not typically used clinically. If both hips are measured, BMD and T-score from each side should be used individually, because there are insufficient data to determine whether mean T-scores for bilateral hip BMD can be used for diagnosis. Forearm BMD can also be obtained in certain circumstances.

6. When should forearm BMD be obtained and which forearm site is clinically relevant?

The forearm is an anatomical site with a high percentage of cortical bone. BMD at the distal 33% radius of the *nondominant* forearm should be obtained if the patient has a disease or condition associated with greater bone loss at primarily cortical sites (e.g., primary hyperparathyroidism), if the patient's weight exceeds the weight limit of the DXA machine, or if other anatomical sites cannot be used or accurately assessed (e.g., presence of hardware). The forearm typically does not respond well to pharmacological therapy (and may even decline with anabolic agents) and is not a preferred site for serial BMD monitoring.

7. When should a vertebra or the entire L-spine be excluded?

A vertebra should be excluded if

- It is clearly anatomically abnormal (e.g., known compression fracture, hardware, etc.)
- There is >1.0 T-score difference between adjacent vertebrae

  A minimum of two vertebrae are required for accurate L-spine BMD assessment.

8. What is a T-score and when should it be used?

A T-score represents the number of standard deviations a person's BMD is above/below the average for young adult, Caucasian, healthy individuals at peak bone mass. It should be used for diagnosis in postmenopausal women and men ≥50 years old. The International Society for Clinical

TABLE 14.2 WHO Classification of BMD (from central DXA)

T-SCORE	DIAGNOSIS
−1.0 or higher	Normal BMD
−1.1 to −2.4	Low Bone Mass (aka Osteopenia)
−2.5 or lower	Osteoporosis

Densitometry (ISCD) recommends that a normative female database be used for generating T-scores in women and men, but some institutions may use a male database to generate T-scores for male patients.

9. What is a Z-score and when should it be used?

A Z-score represents the number of standard deviations a person's BMD is above/below the average of age-, sex-, and sometimes race-matched persons. A Z-score should be used instead of the T-score for diagnosis in premenopausal women and men <50 years old. Z-scores are also informative for postmenopausal women and men ≥50 years of age because a low Z-score (at any age) may indicate an underlying, secondary cause of low bone mass that should be evaluated with history, physical exam, and appropriate laboratory workup.

10. What reference database should be used to generate T- and Z-scores on a DXA exam for transgender or gender-nonconforming individuals?

T-scores for all individuals should be generated using the reference database for young adult Caucasian women and therefore are calculated the same for cisgender, transgender, and gender-nonconforming individuals. For transgender individuals, Z-scores should be calculated using the reference database that matches an individual's gender identity. In gender-nonconforming individuals, Z-scores should be calculated using the reference database for sex assigned at birth. In both transgender and gender-nonconforming individuals, Z-scores may also be calculated and reported with comparisons to both male and female databases, if preferred.

11. What are the cutoffs for an abnormal Z-score?

A Z-score ≤ -2.0 in premenopausal women and men <50 years of age is considered below the expected range for age. Although pharmacologic therapy is sometimes indicated for patients with Z-scores in this range, there is little information available. A decision to treat should be based on a thorough consideration of risks and benefits.

12. What are the cutoffs for an abnormal T-score?

The World Health Organization (WHO) classifications for diagnosing osteoporosis are based on central DXA aBMD measurements and apply to postmenopausal women and men ≥50 years old (Table 14.2). The diagnosis is based on the lowest T-score at the L-spine, total hip, femoral neck, or the 33% radius. For example, if the left total hip T-score is -2.1 and the L1–4 T-score is -2.5 the patient's diagnosis is osteoporosis, not osteopenia at the total hip and osteoporosis at the L-spine. The T-score cutoff of -2.5 is used because it identifies approximately 30% of postmenopausal women as having osteoporosis, which is approximately equivalent to the lifetime risk of fracture at the sites measured. DXA cannot discern why BMD is low. For example, it cannot differentiate osteoporosis from osteomalacia (e.g., inadequate bone mineralization due to vitamin D deficiency, etc.). An appropriate evaluation should be performed to exclude underlying secondary causes of low bone mass, including history, physical exam, and laboratory workup.

It is important to remember that a person can also meet diagnostic criteria for osteoporosis, regardless of BMD, if they have had a fragility fracture, and/or have an elevated fracture risk. Ten-year fracture risk can be estimated using the online Fracture Risk Assessment Tool (FRAX). FRAX can be applied to individuals 40–90 years old. United States FRAX treatment thresholds are ≥20% risk for major osteoporotic fracture and ≥3% risk for hip fracture over the next 10 years. An updated FRAX tool, FRAX Plus, with expanded inputs is available for a fee.

13. How should BMD measurements be used to assess the need for pharmacological treatment in postmenopausal women and men ≥50 years old?

Clinical judgment should be used to determine the need for pharmacological treatment in each individual based on all available data, not just BMD. After appropriate medical evaluation to exclude underlying secondary causes of low BMD, the Endocrine Society and American Association of Clinical Endocrinologists (AACE) suggest pharmacological treatment be considered in postmenopausal women and men ≥50 years old with:

- A T-score ≤-2.5 at the femoral neck, total hip, lumbar spine or 33% radius
- A fragility fracture—defined as a nontraumatic fracture or fracture sustained after a fall from standing height or less that would not otherwise be expected to cause a fracture. Typically applies to a fracture at an osteoporotic site such as the hip, spine, humerus, forearm, and pelvis but not fractures in the face, hands, or feet.
- Low bone mass (T-score of -1.1 through -2.4) with a 10-year risk of major osteoporotic fracture ≥20% or hip fracture ≥3% based on the U.S-adapted FRAX assessment tool.

Nonpharmacological management should also be considered, including fall prevention; smoking cessation; getting adequate amounts of calcium, vitamin D, and protein; and avoiding bone-harming medications and excess alcohol.

14. How should bone density be assessed over time? What is a significant change in BMD?

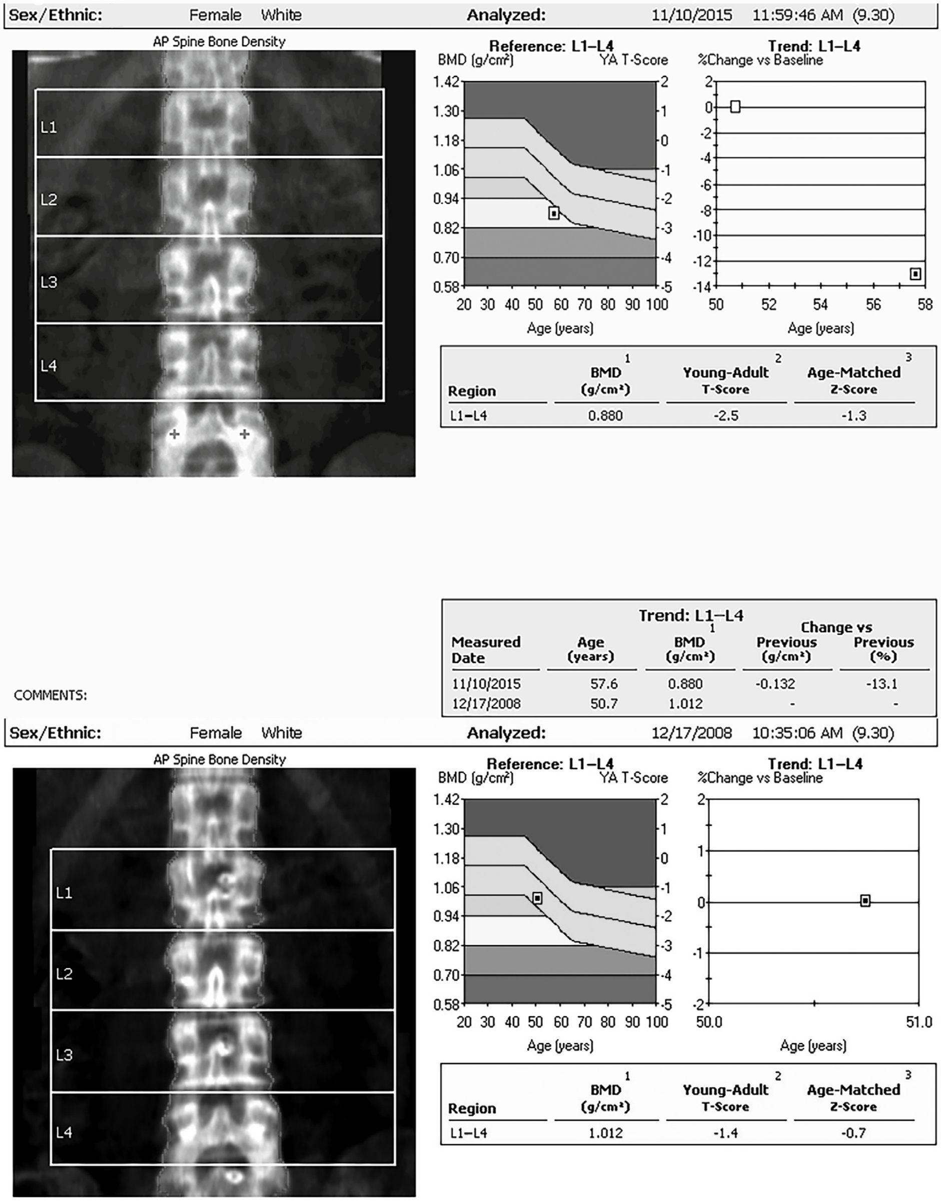
BMD (g/cm^2) should be trended over time, not T- or Z-scores. There are differences in BMD assessment in the various commercially available DXA machines (e.g., Hologic, GE Lunar, Norland). In addition, inherent machine error and differences in patient positioning contribute to measurement error. Therefore only BMD obtained on the same machine at the same facility (ideally performed by the same DXA technician) can be accurately trended over time. A statistically significant change in BMD is one that meets or exceeds the error (i.e., the least significant change [LSC] of the machine. Each DXA facility should report the LSC for their facility/machine/DXA technician for each anatomical site. If not reported, a change >3% is generally considered clinically significant. DXA should be repeated when the change in BMD is expected to exceed the LSC.

15. What anatomical sites are most important for BMD monitoring?

Anatomical sites with a high percentage of trabecular bone (e.g., L-spine) will change the fastest because, compared to cortical bone, trabecular bone has more surface area where bone remodeling occurs. In addition, sites with the best precision of measurement are preferred. Therefore the preferred sites for monitoring (in descending order) are L-spine, total hip, and femoral neck.

16. What are common reasons for inaccurate BMD assessment or BMD trend at the L-spine?

Laminectomy and lytic bone lesions can falsely lower BMD at the L-spine. More commonly, L-spine BMD is artificially increased, particularly in individuals ≥65 years of age. Arthritis, scoliosis, osteophytes, compression fractures, vertebral hemangiomas, internal artifacts overlying lumbar vertebrae (e.g., abdominal aortic calcifications, pill bezoars), hardware or prior spine procedure (e.g., kyphoplasty, vertebroplasty), external artifacts (e.g., naval piercings, buttons on clothing), and osteoblastic bone metastases will falsely increase L-spine BMD and will inflate apparent BMD gains over time at this site. L-spine BMD may not be accurate if a nuclear medicine study or other contrast imaging study has been performed within 1 week of the DXA exam. Vertebral fractures cannot be diagnosed by DXA without Vertebral Fracture Assessment (VFA), therefore follow-up x-rays and/or MRI must be performed if vertebral compression fractures are suspected. Spine imaging is important for diagnosing compression fractures because approximately 50% of vertebral fractures are clinically silent. DXA images should be evaluated to ensure L1-L4 are accurately labeled and that the same vertebral levels are assessed over time (Fig. 14.1).



Sex/Ethnic: Female White **Analyzed:** 11/10/2015 11:59:46 AM (9.30)

AP Spine Bone Density
L1
L2
L3
L4
Reference: L1–L4
BMD (g/cm²)
YA T-Score
1.42
1.30
1.18
1.06
0.94
0.82
0.70
0.58
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age (years)
Trend: L1–L4
%Change vs Baseline
2
0
-2
-4
-6
-8
-10
-12
-14
50 52 54 56 58
Age (years)

Region	BMD (g/cm²) [1]	Young-Adult T-Score [2]	Age-Matched Z-Score [3]
L1–L4	0.880	-2.5	-1.3

COMMENTS:

Trend: L1–L4

Measured Date	Age (years)	BMD (g/cm²) [1]	Change vs Previous (g/cm²)	Change vs Previous (%)
11/10/2015	57.6	0.880	-0.132	-13.1
12/17/2008	50.7	1.012	-	-

Sex/Ethnic: Female White **Analyzed:** 12/17/2008 10:35:06 AM (9.30)

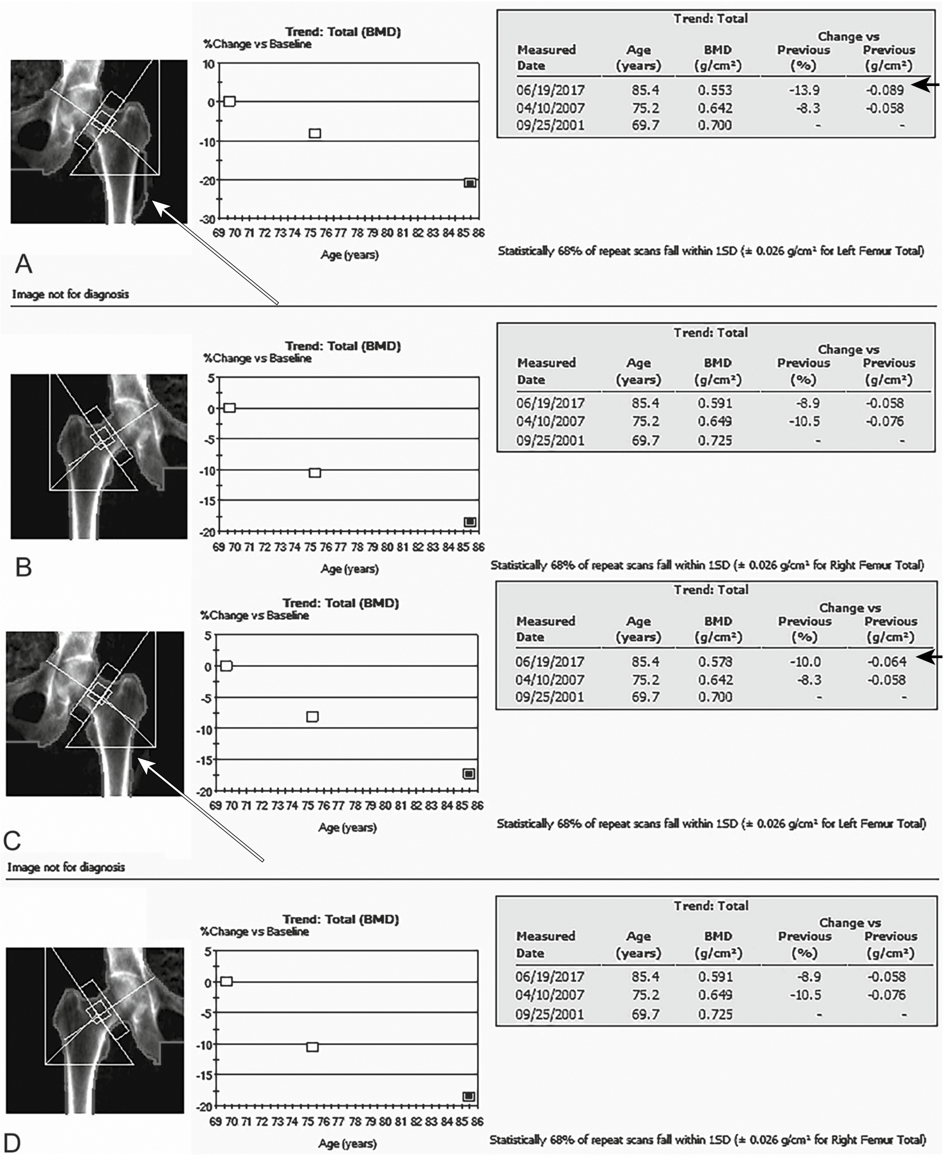
AP Spine Bone Density
L1
L2
L3
L4
Reference: L1–L4
BMD (g/cm²)
YA T-Score
1.42
1.30
1.18
1.06
0.94
0.82
0.70
0.58
2
1
0
-1
-2
-3
-4
-5
20 30 40 50 60 70 80 90 100
Age (years)
Trend: L1–L4
%Change vs Baseline
2
1
0
-1
-2
50.0
51.0
Age (years)

Region	BMD (g/cm²) [1]	Young-Adult T-Score [2]	Age-Matched Z-Score [3]
L1–L4	1.012	-1.4	-0.7

Fig. 14.1 Example of Erroneous Lumbar Spine (L-Spine) BMD Loss. DXA in a 57-year-old female showed 13.1% BMD loss at the L-spine (top) compared to prior exam performed 7 years earlier (bottom). Bone loss is erroneous because different vertebral levels were assessed in the two exams. The vertebrae measured in the top image are one vertebral level higher than in the bottom image.

17. What are common reasons for inaccurate BMD assessment or BMD trend at the total hip?

Overlying clothing artifact and differences in hip rotation, femur angle (excessive femur abduction/adduction), and ROI placement can alter accurate BMD assessment and trend over time (Fig. 14.2). The femur should be internally rotated 15–20° so that the lesser trochanter is barely seen, if at all. If the lesser trochanter is seen, subsequent exams should match the degree of rotation on previous exams to avoid artifactual changes in BMD. Except in rare circumstances,


Trend: Total (BMD)
%Change vs Baseline
10
0
-10
-20
-30
69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86
Age (years)
A
Image not for diagnosis

Trend: Total

Measured Date	Age (years)	BMD (g/cm²)	Change vs Previous (%)	Change vs Previous (g/cm²)
06/19/2017	85.4	0.553	-13.9	-0.089
04/10/2007	75.2	0.642	-8.3	-0.058
09/25/2001	69.7	0.700	-	-

Statistically 68% of repeat scans fall within 1SD (± 0.026 g/cm² for Left Femur Total)

Trend: Total (BMD)
%Change vs Baseline
5
0
-5
-10
-15
-20
69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86
Age (years)
B

Trend: Total

Measured Date	Age (years)	BMD (g/cm²)	Change vs Previous (%)	Change vs Previous (g/cm²)
06/19/2017	85.4	0.591	-8.9	-0.058
04/10/2007	75.2	0.649	-10.5	-0.076
09/25/2001	69.7	0.725	-	-

Statistically 68% of repeat scans fall within 1SD (± 0.026 g/cm² for Right Femur Total)

Trend: Total (BMD)
%Change vs Baseline
5
0
-5
-10
-15
-20
69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86
Age (years)
C
Image not for diagnosis

Trend: Total

Measured Date	Age (years)	BMD (g/cm²)	Change vs Previous (%)	Change vs Previous (g/cm²)
06/19/2017	85.4	0.578	-10.0	-0.064
04/10/2007	75.2	0.642	-8.3	-0.058
09/25/2001	69.7	0.700	-	-

Statistically 68% of repeat scans fall within 1SD (± 0.026 g/cm² for Left Femur Total)

Trend: Total (BMD)
%Change vs Baseline
5
0
-5
-10
-15
-20
69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86
Age (years)
D

Trend: Total

Measured Date	Age (years)	BMD (g/cm²)	Change vs Previous (%)	Change vs Previous (g/cm²)
06/19/2017	85.4	0.591	-8.9	-0.058
04/10/2007	75.2	0.649	-10.5	-0.076
09/25/2001	69.7	0.725	-	-

Statistically 68% of repeat scans fall within 1SD (± 0.026 g/cm² for Right Femur Total)

Fig. 14.2 Asymmetric BMD Change at Bilateral Total Femurs. Relatively greater BMD loss at the left total hip compared to right total hip from 2007 to 2017 (A, B). When the red region of interest (ROI) line is correctly drawn on the left femur to more closely approximate the bone (*long arrows in A/C*), the magnitude of BMD loss at the left hip changes (*short arrows*) and is now more symmetric at the right and left total hips (C,D).

osteoarthritis at the hip joint does not affect BMD assessment at the total hip. The hip should be excluded if hardware is present.

18. What is TBS and when should it be used?

Trabecular Bone Score (TBS) software analyzes pixel gray-level variations in the AP L-spine DXA image (in real time or on a previously obtained scan) to assess trabecular microarchitecture, an important determinant of bone strength (Fig. 14.3). TBS is a unitless number

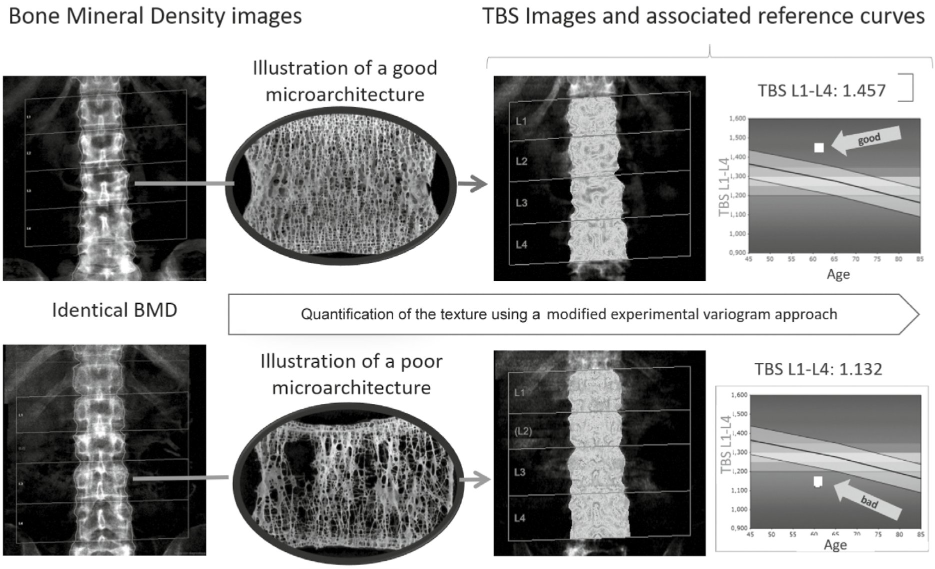

Bone Mineral Density images
TBS Images and associated reference curves
Illustration of a good microarchitecture
TBS L1-L4: 1.457
good
L1
L2
L3
L4
TBS L1-L4
Age
Identical BMD
Quantification of the texture using a modified experimental variogram approach
Illustration of a poor microarchitecture
TBS L1-L4: 1.132
bad
(L2)
1,600
1,500
1,400
1,300
1,200
1,100
1,000
0,900
45
50
55
60
65
70
75
80
85

Fig. 14.3 Sample TBS from Ulivieri, et al. Endocrine 2014 47:435–48. Difference in TBS/microarchitecture for two women with the same lumbar spine BMD. The woman with lower TBS would have a higher fracture risk than the woman with a higher TBS.

TABLE 14.3 Trabecular Bone Score (TBS) Cutoffs

TBS	DIAGNOSIS
>1.310	Normal Bone Microarchitecture
1.230–1.310	Partially Degraded Bone Microarchitecture
<1.230	Degraded Bone Microarchitecture

As per USA NHANES/Medimaps Reference Curves for Non-Hispanic White and Black Men and Women and Mexican-American Men and Women published in McCloskey, et al. JBMR 2015.

that classifies a person's bone microarchitecture as normal, partially degraded, or degraded (Table 14.3). As a rough estimate of bone quality, TBS predicts fracture risk independent of BMD and is associated with vertebral, hip, and major osteoporotic fracture risk in postmenopausal women, major osteoporotic fracture risk in postmenopausal women with Diabetes Mellitus Type 2, and risk of hip and major osteoporotic fractures in men ≥50 years old. Treatment decisions should not be based on TBS alone; however, FRAX fracture risk assessments can be adjusted for L1–4 TBS. TBS is potentially useful for monitoring the response to some osteoporosis pharmacologic therapies.

19. What additional considerations are needed for BMD assessment in children?

DXA assessment in children is typically performed at the L-spine and total body (minus head). T-scores should not be used in this population because aBMD is dependent on bone size, and children have not reached peak bone mass. Bone mineral apparent density (BMAD in g/cm^3) can estimate vBMD at the L-spine and femoral neck to overcome the limitations of bone size in a 2D DXA image. Osteoporosis diagnosis should not be made based on BMD alone and requires clinical context in younger populations.

KEY POINTS

- aBMD from central DXA is the clinical gold standard for assessing bone density.
- T-scores are preferentially used to diagnose low bone mass and osteoporosis in postmenopausal women and men ≥50 years old, but Z-scores can still provide insight on possible underlying causes of low bone mass and osteoporosis.
- DXA cannot establish why BMD is low—an appropriate medical evaluation to exclude secondary causes of osteoporosis (e.g., osteomalacia) should be performed.
- Review of DXA images is critical to ensuring BMD assessment and trend are accurate.
- TBS is an assessment of trabecular bone microarchitecture using the L-spine DXA image and can be used to augment fracture risk assessment and treatment decisions.

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Osteoporosis Management

Michael T. McDermott

1. What nonpharmacologic measures help to prevent and treat osteoporosis?

Adequate calcium intake (diet plus supplements):*
  1000–1200 mg/day, premenopausal women and men.
  1200–1500 mg/day, postmenopausal women and men ≥age 65 years.
Adequate Vitamin D intake: 800–1200 IU/day.
Regular exercise: aerobic and resistance.
Limitation of alcohol consumption to ≤2 drinks/day.
Limitation of caffeine consumption to ≤2 servings/day.
Smoking cessation.
Fall prevention.

Note: Taking more than the stated amounts of calcium and vitamin D is not recommended. Higher intakes may be associated with kidney stones as well as more vascular calcifications, particularly in patients with renal insufficiency.

2. How can dietary calcium intake be accurately assessed?

The major bioavailable sources are dairy products and calcium-fortified fruit drinks. The following approximate calcium contents should be assigned for dairy product intake:

Milk/Yogurt	300 mg/cup
Cheese	300 mg/oz
Fruit juice with calcium	300 mg/cup

Add another 300 mg for the general nondairy diet for a reasonable estimate of total daily calcium intake.

3. How do you ensure adequate intake of calcium?

Low-fat dairy products are the *best* sources of calcium. Calcium supplements should be added when the desired goals cannot be reached with dietary sources. Calcium carbonate and calcium citrate are both well absorbed when taken with meals. Gastric acid is needed for normal calcium absorption; calcium carbonate absorption may be significantly reduced in patients who have achlorhydria or who use a proton pump inhibitor (PPI). Calcium citrate absorption is less likely to be affected by PPI use. Calcium citrate is also a better choice in patients with a history of kidney stones since citric acid is often low in the urine of stone formers.

4. What are the best ways to achieve adequate vitamin D intake?

Vitamin D exists in two natural forms: cholecalciferol (D_3) and ergocalciferol (D_2). Fatty fish (salmon, tuna, mackerel; D_3 = 400 IU/3.5oz), fortified milk (400 IU/quart), and cereal products (50 IU/cup) are good dietary sources. Vitamin D_2 and D_3 supplements are available over the counter in multiple doses, and 50,000 IU vitamin D_2 supplements can be given by prescription. Ten minutes of midday summer sunlight exposure to a fair-skinned person in a tank-top and shorts not wearing sunscreen produces 10,000 IU of vitamin D_3. Dark-skinned individuals and the elderly get less production. However, many individuals wear sunscreen (SPF >8), which prevents vitamin D production by the skin. Therefore oral vitamin D is necessary for most people. The optimal vitamin D intake is 800–1200 IU daily and should not exceed 4000 IU/day chronically.

5. How do you treat patients with vitamin D deficiency?

The goal serum 25 OH vitamin D level is 30–100 ng/ml. In general, 1000 units (U) daily of vitamin D will raise the serum level by 6–10 ng/ml. I recommend the following:

25 OH D Level	*Management*
20–30 ng/ml	2000 U D3 daily
10–20 ng/ml	50,000 U D2 weekly for 3 months, then 2000 U D3 daily
<10 ng/ml	50,000 U D2 twice weekly for 3 months, then 2000 U D3 daily

Patients with malabsorption syndromes, bowel bypass surgery, and severe liver disease and those who take antiepileptic drugs may require higher doses. Some may need to be treated with calcitriol. Obese patients, because of their larger volume of distribution of this fat-soluble vitamin, may require higher doses or longer durations of treatment. However, noncompliance is the most common reason that patients with persistently low vitamin D levels on therapy do not increase their levels.

6. Does calcium or vitamin D supplementation promote vascular calcification or coronary artery disease?

The suggestion that calcium and/or vitamin D supplementation promotes calcification of coronary arteries arose from several early, small studies that gained significant lay press attention. However, subsequent large reviews and meta-analyses demonstrated that the existing published evidence does not support the hypothesis that calcium and/or vitamin D supplementation, in recommended doses, increases the risk of coronary artery disease (CAD) or CAD mortality. As stated above, however, excessive doses should be avoided.

7. When should pharmacological therapy be initiated for osteoporosis?

Pharmacological therapy should be advised for patients who have any *one* of the following:

- Fragility Fracture (vertebral, hip, wrist, humerus)
- T-Score ≤-2.5 (at any site)
- FRAX 10 Year Risk ≥3% for hip fracture or ≥20% for major osteoporosis fractures

The FRAX tool (Search Engine: FRAX), developed by the World Health Organization (WHO), is recommended for making treatment decisions in drug naïve patients with osteopenia on BMD testing.

8. Describe bone remodeling.

Bone remodeling is the process that removes old bone and replaces it with new bone. Osteoclasts attach to bone surfaces and secrete acid and enzymes that erode underlying bone. Osteoblasts then migrate into these resorption pits and secrete osteoid, which becomes mineralized with calcium phosphate crystals (hydroxyapatite). Osteocytes serve as the mechanoreceptors that sense skeletal stress and send signals, such as sclerostin, to orchestrate the process of bone remodeling in areas of bone that need renewal. See Fig. 15.1.

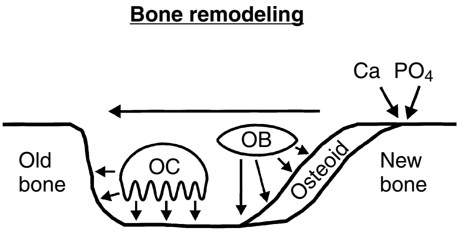

Fig. 15.1 Bone remodeling. *OC* = Osteoclast, *OB* = Osteoblast

9. What are RANK, RANK-L, and Osteoprotegerin?

RANK (receptor activator of nuclear factor κ) is a receptor on osteoclasts. RANK-L (RANK ligand) binds to RANK to stimulate osteoclastic bone resorption. Osteoprotegerin (OPG) is a soluble decoy receptor produced by osteoblasts and bone marrow stromal cells that binds to RANK-L, preventing it from binding to RANK. Bone resorption is driven by RANK-L and inhibited by OPG.

10. How do the pharmacological agents for osteoporosis work?

Osteoporosis medications are classified into two main categories: *antiresorptive* agents and *anabolic* agents. Antiresorptive medications include bisphosphonates, denosumab, estrogens, raloxifene, and calcitonin; they inhibit osteoclastic bone resorption. Teriparatide and abaloparatide are anabolic agents; they stimulate osteoblastic bone formation. Romosozumab has both anabolic and antiresorptive actions.

11. What pharmacological agents are FDA approved and how are they used?

Mechanism	***Route***	***Dose***	***Frequency***
Antiresorptive Agents			
Bisphosphonates			
Alendronate (Fosamax)	Oral	10 mg	Daily
		70 mg	Weekly
Risedronate (Actonel)	Oral	5 mg	Daily
		35 mg	Weekly
		150 mg	Monthly
Risedronate SR (Atelvia)	Oral	35 mg	Weekly
Ibandronate (Boniva)	Oral	150 mg	Monthly
	IV	3 mg	Q3 Months
Zoledronic Acid (Reclast)	IV	5 mg	Yearly
Nonbisphosphonates			
Denosumab (Prolia)	SQ	60 mg	Q6 Months
Raloxifene (Evista)	Oral	60 mg	Daily
Calcitonin (Miacalcin)	Nasal	200 U	Daily
	SQ[+]	100 U	Daily
Estrogen Therapy (multiple preparations and regimens)			
Anabolic Agents			
Teriparatide (Forteo)	SQ[+]	20 mcg	Daily (prolonged use approved)
Abaloparatide (Tymlos)	SQ	80 mcg	Daily (18–24 months)
Combination Agent			
Romosozumab (Evenity)	SQ	210 mg	Monthly (1 year)

[+] Infusion times: IV ibandronate 1–3 minutes; IV zoledronic acid 15–60 minutes.
SR = Slow release, *IV* = Intravenous, *SQ* = Subcutaneous

12. Explain how bisphosphonates work.

Bisphosphonates are pyrophosphate analogues that avidly bind to bone and are subsequently ingested by osteoclasts during bone remodeling. They inhibit osteoclast function by blocking the enzyme, farnesyl diphosphate synthase (FPPS), in the HMG CoA-reductase (mevalonate) pathway. FPPS inhibition prevents the formation of essential metabolites (Ras, Rho, Rac) that normally connect small proteins to the cell membrane, a process known as prenylation, which is critical for subcellular protein trafficking. This interferes with the lipid modification of the osteoclast cell membrane and cytoskeleton that is required for maintenance of the "ruffled border," resulting in impaired osteoclast activity and accelerated osteoclast apoptosis. Since bone formation is not initially affected, bone formation temporarily exceeds resorption, and bone mass increases. After about 24 months, bone formation declines to the level of resorption, and bone mass stabilizes. Over this time bone mass increases 4–8% in the spine and 3–6% in the hip. This is accompanied by a 33–68% relative risk reduction for incident vertebral fractures (all agents) and a 40–50% reduction in hip fractures (alendronate, risedronate, and zoledronic acid only).

13. Describe how bisphosphonates should be taken.

Bisphosphonates have poor intestinal absorption (<1%) that is further inhibited by the presence of food or medications in the intestinal tract. The major side effect of oral bisphosphonates is esophageal and gastrointestinal pain. In order to maximize intestinal absorption and minimize gastrointestinal toxicity, they should be taken first thing each morning on an empty stomach with a full glass of water. The patient should then remain upright and take nothing by mouth for 30–60 minutes after medication ingestion. Gastrointestinal side effects can be avoided and adherence improved with the use of intravenous bisphosphonates.

Due to the risk of osteonecrosis of the jaw (ONJ) with antiresorptive therapies, providers should do an oral examination before starting a bisphosphonate, and any planned invasive dental work (extractions, implants) should be done prior to starting a bisphosphonate.

14. What is Denosumab and how does it work in osteoporosis?

Denosumab is a monoclonal antibody directed against RANK-L, which is expressed on the surface of osteoblasts. Denosumab prevents RANK-L from binding to RANK to stimulate osteoclastic bone resorption. Denosumab increased lumbar spine bone mass 6.5% and hip mass by 3.5% in clinical trials. This was accompanied by a 68% reduction in vertebral and 40% reduction in hip fractures over 3 years. Denosumab is cleared by the reticuloendothelial system and can therefore be used in people with stage 4 chronic kidney disease (eGFR 15–30 cc/min). It is given as 60 mg subcutaneously (SQ) every 6 months in a clinic or an infusion center. This medication is well tolerated, but there is concern that infections could be increased, since RANK-L is also expressed on T helper cells and involved in dendritic cell activation.

Because of the risk of osteonecrosis of the jaw (ONJ) with antiresorptive therapies, any planned invasive dental work (extractions, implants) should be done prior to starting Denosumab, if possible. It is also recommended that providers do an oral examination before starting Denosumab therapy.

15. What happens when Denosumab is stopped and what precautions are recommended?

Discontinuation of Denosumab has been reported to result in rapid bone loss and development of multiple vertebral fractures in some people. If Denosumab is stopped after at least two doses, it is recommended that bisphosphonate therapy be started; IV Zoledronic Acid should be given 6–9 months after the last Denosumab injection or an oral bisphosphonate started 6 months after the last injection.

16. What is osteonecrosis of the jaw (ONJ) and which medications may cause it?

ONJ presents as persistently exposed nonhealing bone following an invasive dental procedure (extractions, implants); it does not occur after root canal procedures or fillings. It has been reported mainly with strong antiresorptive drugs (bisphosphonates, denosumab) and does not occur with anabolic bone agents. ONJ develops most often during high-dose, frequent administration of antiresorptive agents for the treatment of multiple myeloma or bone metastases; however, it has also been reported, though less often, in people taking these agents for osteoporosis. Good oral hygiene and regular dental care are the best preventive measures. An oral exam should be done by the prescribing provider prior to starting an antiresorptive medication. Temporarily stopping antiresorptive therapy for invasive dental procedures (3 months prior) is a common and reasonable practice but has not been proven to prevent ONJ. Some oral surgeons require a serum C-telopeptide to be in the normal range before they will do surgery.

17. What about atypical femoral fractures with antiresorptive medication use?

Atypical femoral fractures (AFF) have also been reported with use of antiresorptive agents; anabolic drugs have not been implicated as causative agents. AFF have occurred almost exclusively with long-term antiresorptive therapy (>5 years). Unexplained thigh pain in a person on antiresorptive drugs should be evaluated with a radiograph looking for a "bird-beak" on the lateral aspect of the femoral shaft, indicating a stress fracture (Fig. 15.2). These fractures are often bilateral and require femoral rods to stabilize. The risk is low (1 in 2000 patients) but appears increased in active people, those on corticosteroids, and those with very low bone turnover markers.

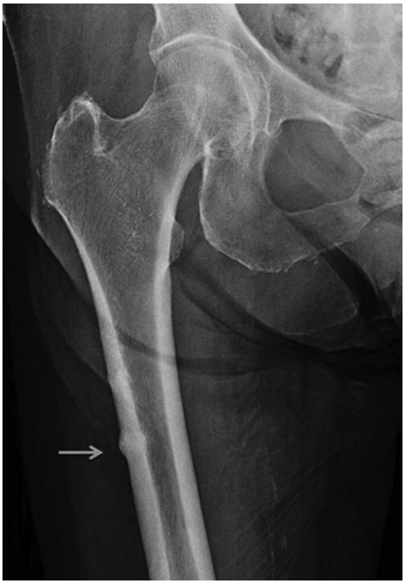

Fig. 15.2 Characteristic radiographic features of an atypical femur fracture.

Periodic drug holidays for people on bisphosphonates are recommended by many providers to reduce the risk of AFF. The optimal durations of bisphosphonate therapy before considering a drug holiday are shown in questions 27 and 28. A drug holiday decreases the risk for AFF by 70%. Drug holidays are not currently recommended for denosumab because of the rapid bone loss and vertebral fractures that have been reported in some patients after discontinuation of this medication.

18. Briefly discuss the issues regarding estrogen replacement therapy (ERT) hormone replacement therapy (HRT).

The Women's Health Initiative (WHI) report in 2002 affirmed the efficacy of ERT (estrogen) and HRT (estrogen plus progesterone) for fracture prevention but also confirmed a previously reported increased risk of breast cancer and cardiovascular events. After this report, ERT and HRT use significantly declined. Subsequent studies cast serious doubt on the risk of these adverse events with ERT and HRT, especially ERT. Currently ERT (women without an intact uterus) and HRT (women with an intact uterus) are recommended mainly for limited use for up to 3 years to treat postmenopausal hot flashes, but more prolonged use is appropriate at the discretion of the provider after a thorough discussion and shared decision-making.

19. Discuss selective estrogen receptor modulators (SERMS) for management of osteoporosis.

Selective estrogen receptor modulators (SERMS) function as estrogen agonists in some tissues (bone) and estrogen antagonists in others (breast). Raloxifene is FDA approved for treatment of postmenopausal osteoporosis. In clinical trials, BMD increased by 2–3% in the spine and hip and the relative risk of vertebral fractures decreased by 31–49% with no effect on hip fractures. Raloxifene also reduces the risk of developing invasive breast cancer (76%). The dose is 60 mg daily. Side effects include hot flashes, leg cramps, and an increased risk of thromboembolic disease (especially in smokers), similar to that seen with HRT. An ideal person to consider for raloxifene is someone with osteoporosis and a personal or family history of breast cancer.

20. How can PTH and PTHrP be anabolic agents for treating osteoporosis?

Persistently elevated serum parathyroid hormone (PTH) (hyperparathyroidism) or parathyroid hormone related peptide (PTHrP) levels promote bone resorption, hypercalcemia, and bone loss. In contrast, intermittent daily pulses of exogenous PTH or PTHrP actually stimulate osteoblast differentiation, proliferation, and survival, resulting in osteoid formation and increased bone mass. They also decrease production of the bone formation inhibiting protein, sclerostin, by osteocytes.

21. Describe the currently available osteo-anabolic agents?

Teriparatide is a 34 amino acid fragment of intact PTH that binds to and activates PTH receptors on osteoblasts and precursors. It is self-administered SQ as a 20 mcg/day dose for 18–24 months but prolonged use is now approved. In trials, teriparatide increased lumbar spine BMD 9–13% and hip BMD 2.5–5% and reduced the relative risk of new vertebral fractures 65% and nonvertebral fractures 50%. Side effects were similar to placebo: headache, nausea, arthralgias, orthostasis, flushing. Teriparatide requires refrigerated for the duration of its use; it becomes inactivated if left unrefrigerated for over 24 hours.

Abaloparatide is a 34 amino acid fragment of PTHrP that also activates osteoblast recruitment and activity. It is self-injected as an 80 mcg SQ daily dose for up to 24 months. Spine BMD has been shown to increase by 10.4% and hip BMD by 4% compared to placebo. In a head-to-head trial against teriparatide, abaloparatide reduced new vertebral fractures by 86%, nonvertebral fractures by 43%, and major osteoporosis fractures by 70% (the latter was statistically significantly better than teriparatide). Side effects are similar to those of teriparatide. Abaloparatide does not require refrigeration.

Romosozumab is a monoclonal antibody directed against sclerostin, an intrinsic inhibitor of the WNT pathway that stimulates bone formation. By inhibiting the inhibitor (sclerostin) of bone formation, romosozumab stimulates bone formation and therefore is an anabolic agent. Through other mechanisms it also inhibits bone resorption resulting in dual anabolic and antiresorptive activity. Romosozumab is administered in an infusion center or office as a 210 mg SQ dose once every month for 1 year. Compared to placebo, romosozumab increased BMD 12.7% in the lumbar spine, 5.8% in the total hip, and 5.2% in the femoral neck and reduced vertebral fractures by 73%. The most common side effects in clinical trials were joint pain and headaches. Serum calcium levels often decrease transiently after administration. Both ONJ and AFF have been reported with romosozumab. Serious adverse events in clinical trials included strokes, myocardial infarctions and cardiovascular deaths. As a result, it is recommended that romosozumab be avoided in people who have had a stroke or major cardiovascular event within the past year and in those at high risk of stroke or cardiovascular disease.

22. Discuss the role of testosterone for the treatment of osteoporosis?

Men with osteoporosis and symptoms of hypogonadism may benefit from testosterone replacement therapy (TRT), especially if the serum testosterone level is less than 150 ng/dL. Testosterone replacement increases bone mass in men with baseline low testosterone levels, but there has been no fracture reduction data reported; for this reason, it is not an FDA approved treatment for osteoporosis.

Testosterone cypionate or enanthate can be administered intramuscularly (IM) (100–400 mg every 1–4 weeks; lower doses at more frequent intervals are preferred), as a transdermal patch (AndroDerm) or gel (Testim, AndroGel, Fortesta, Axiron, Vogelxo), as a buccal patch (Striant), testosterone undecanoate (oral or IM), or testosterone pellets. We do not recommend injectable testosterone pellets because supraphysiological testosterone levels often result from this therapy. TRT has not been shown to cause prostate cancer but has clearly been shown to increase the risk of growth of existing prostate cancer. TRT can also precipitate or worsen sleep apnea. The TRAVERSE study, a large multicenter randomized controlled trial of TRT in hypogonadal men with preexisting or a high risk of cardiovascular disease, reported in 2023 that physiologic testosterone doses do not promote the development of cardiovascular disease.

23. Have all these medications been shown to prevent fractures?

The FDA-approved medications have all been demonstrated in randomized controlled trials (RCTs) to significantly reduce vertebral fractures in women with postmenopausal osteoporosis. Hip fractures have also been reduced by alendronate, risedronate, zoledronic acid, and denosumab. Nonvertebral fracture reduction has been reported with alendronate, risedronate, zoledronic acid, denosumab, teriparatide, and abaloparatide.

24. Should osteoporosis medications be used in combination?

Combining two antiresorptive drugs should be avoided to prevent oversuppression of bone remodeling. Combining anabolic and antiresorptive drugs is an appealing notion currently under investigation. Teriparatide combined with alendronate showed inferior BMD gains compared to teriparatide alone. However, teriparatide plus zoledronic acid or denosumab did show synergy for BMD improvement. Despite promising BMD results, there are no data for superior fracture reduction compared to monotherapy, and therefore combination therapy is not currently recommended. Furthermore, the cost of two drugs is additive and not usually approved for insurance coverage. Sequential therapy, however, is clearly beneficial and is supported by a strong evidence base. Leaders in the field suggest that people with severe osteoporosis may have maximal benefit by receiving anabolic therapy first, followed by an antiresorptive agent.

25. Summarize the benefits and risks of the FDA approved osteoporosis drugs.

BENEFITS

Fracture Reduction (significant for all FDA approved agents)

RISKS

Common Side Effects
Upper GI Symptoms—oral bisphosphonates
Acute Phase Reactions—IV bisphosphonates (1st dose)
Transient serum calcium decrease—zoledronic acid, denosumab, romosozumab
Transient increase in serum and urine calcium—teriparatide, abaloparatide
Uncommon / Rare Side Effects
Osteonecrosis of the Jaw—antiresorptive agents
Atypical Femoral Fractures—antiresorptive agents
Uveitis, Keratitis, Optic Neuritis, Orbital Swelling—bisphosphonates
Hypercalcemia—teriparatide, abaloparatide
Stroke, Myocardial Infarction—romosozumab

26. Describe a risk stratification strategy for planning osteoporosis therapy.

LOW/MODERATE FRACTURE RISK

Oral Bisphosphonates (alendronate, risedronate, ibandronate)
Zoledronic Acid
Denosumab

HIGH FRACTURE RISK*

Zoledronic Acid
Denosumab
Teriparatide
Abaloparatide
Romosozumab

27. What is the optimal duration of treatment with osteoporosis medications?

Oral Bisphosphonates
- 5 years (low/moderate fracture risk)
- 6–10 years (high fracture risk*)

Zoledronic Acid
- 3 years (low/moderate fracture risk)
- 6 years (high fracture risk*)
- Denosumab—indefinite/uncertain**
- Teriparatide—2 years; prolonged use approved**
- Abaloparatide—2 years**
- Romosozumab—1 year**

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* High Risk: old age, prior fracture, very low BMD, high fall risk, glucocorticoid use.

*High Risk: old age, prior fracture, very low BMD, high fall risk, glucocorticoid use.

** Stopping is not recommended without substituting another agent.

28. What about osteoporosis drug holidays? Who and when?

Bisphosphonates are the only osteoporosis medications for which drug holidays should be considered. Drug holidays are not recommended with denosumab, teriparatide, or abaloparatide because of rapid bone loss after their discontinuation; when these medications are stopped, another agent should be substituted.

Bisphosphonate drug holidays may be considered after an optimal treatment course (see above). Bisphosphonate drug holidays should end when:

- Fragility fracture (spine, hip, wrist, humerus) occurs.
- Bone density decreases more than the least significant change (LSC) established for that specific instrument (see discussion of LSC below).
- Bone turnover markers (serum c-telopeptide, serum bone specific alkaline phosphatase) rise by ≥30% or into the upper 50% of the reference range.

29. How should BMD testing be used to monitor the response to therapy?

BMD monitoring of therapy responses is usually repeated in 1–2 years. For accurate interpretation of serial changes, BMD must be measured on the same instrument and the least significant change (LSC) for that specific instrument must be reported.

The LSC is a precision estimate that informs the user about the minimum significant BMD change. Procedures for LSC assessment are available on the International Society for Clinical Densitometry website, www.iscd.org.

30. How do you interpret BMD changes in people on osteoporosis medications?

BMD Change	*Interpretation*	*Recommended Action*
Increase ≥LSC	Good Response	Continue Therapy
No Change or <LSC	Adequate Response	Continue Therapy
Decrease ≥LSC	Treatment Failure	Evaluate; Consider Therapy Change

BMD, Bone mineral density, *LSC*, Least significant change

31. What bone remodeling biomarkers are available and how are they used?

Bone Formation	*Bone Resorption*
Serum Alkaline Phosphatase	Serum C-telopeptides
Serum Osteocalcin	Urine or Serum N-telopeptides
Serum P1NP	

P1NP, Procollagen Type I N-Terminal Propeptide

Biomarker elevation predicts future bone loss. A 30% biomarker reduction on therapy verifies compliance and predicts a BMD increase.

Note: Marked variability in biomarker measurement limits the utility of this tool.

32. What constitutes a treatment failure to osteoporosis therapy?

This is controversial because no treatment completely eliminates the fracture risk since these people are already at high fracture risk.

Criteria for treatment failure (suggested)—any of these, while on treatment:

1. Two or more fragility fractures
2. BMD decrease ≥LSC on the same BMD instrument
3. Remodeling biomarkers h 30% or in the upper 1/2 of the reference range

33. What should be done when BMD declines on osteoporosis therapy?

The common causes of BMD loss on treatment and their management are listed below:

Cause	*Management*
NonAdherence →	Encourage Adherence
Calcium Deficiency →	Adequate Calcium Intake
Vitamin D Deficiency →	Adequate Vitamin D Intake
Secondary Bone Loss →	Treat the Cause
Treatment Failure →	Change Medication

34. Which medications are recommended for prevention and treatment of glucocorticoid-induced osteoporosis (GIOP)?

The 2022 American College of Rheumatology (ACR) guidelines endorse bisphosphonates, denosumab, teriparatide, abaloparatide, romosozumab, and raloxifene strongly, usually or conditionally (under specified circumstances) for GIOP prevention and treatment depending on the individualized fracture risk category based on age, FRAX, BMD, fracture history, and glucocorticoid (GC) dose. Adequate calcium and vitamin D intake and regular exercise, as tolerated, are recommended for all people treated with GC.

35. When should osteoporosis (OP) medications be considered in people over age 40 years who are taking glucocorticoid therapy?

The risk-stratified 2022 ACR recommendations for GIOP prevention and treatment in people over age 40 years are the following:

Low Fracture Risk: OP medications not recommended.

Moderate Fracture Risk: recommend for bisphosphonates, denosumab, teriparatide, abaloparatide, or raloxifene; conditionally recommend against romosozumab except in people intolerant of all other OP medications due to risk of myocardial infarction, stroke, or death.

High Fracture Risk: recommend for denosumab, teriparatide, or abaloparatide over bisphosphonates; recommend bisphosphonates over no treatment; conditionally recommend romosozumab or raloxifene in people intolerant of all other OP medications.

Very High Fracture Risk: conditionally recommend teriparatide or abaloparatide over antiresorptive therapy; recommend denosumab or bisphosphonates over no treatment; conditionally recommend romosozumab or raloxifene in people intolerant of all other OP medications.

Receiving High-Dose GC (initial dose ≥30 mg/day for >30 days or cumulative dose ≥5 g in 1 year): conditionally recommend teriparatide or abaloparatide over antiresorptive therapy; strongly recommend oral bisphosphonates over no treatment; conditionally recommend IV bisphosphonates and denosumab over no treatment; conditionally recommend romosozumab or raloxifene in people intolerant of all other OP medications.

People With Organ Transplants, eGFR ≥35 ml/min, and No Evidence of Renal Osteodystrophy or Hyperparathyroidism: conditionally recommend expert evaluation for renal osteodystrophy in kidney transplant recipients; conditionally recommend bisphosphonates, denosumab, teriparatide, abaloparatide, or raloxifene based on individual patient factors; conditionally recommend against romosozumab due to risk of myocardial infarction, stroke, or death.

36. How do the 2022 ACR recommendations for GIOP prevention and treatment differ for people under age 40 years?

Moderate Fracture Risk: conditionally recommend bisphosphonates, denosumab, teriparatide, or abaloparatide; conditionally recommend against romosozumab and raloxifene due to potential harmful effects.

37. How should you evaluate and manage people on intermittent or inhaled GC therapy?

Guidelines for GIOP prevention/treatment in people receiving intermittent GC therapy are lacking. Those receiving ≥4 monthly IV pulses (1 g methylprednisolone equivalent) or high-dose oral pulses (prednisone ≥60 mg/d with taper over 2–4 weeks) within a 12-month period are at risk and should be considered for treatment. People on daily inhaled steroids (Advair 200 ug/d equivalent or higher dose) for a prolonged period can also lose significant BMD and should be periodically monitored.

38. Develop an algorithm for the diagnosis and management of osteoporosis

See Fig. 15.3.

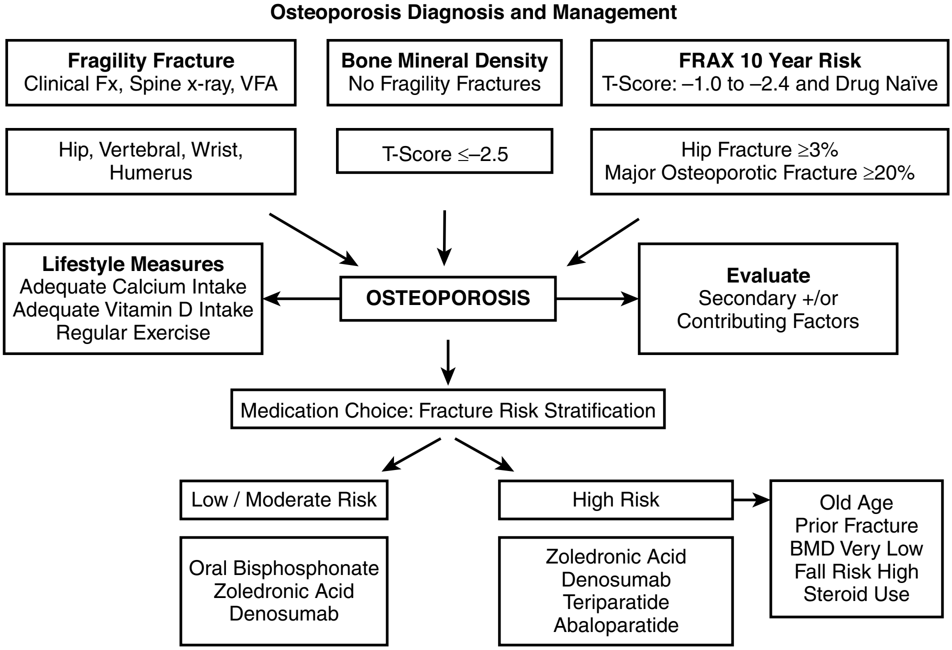
Osteoporosis Diagnosis and Management
Fragility Fracture
Clinical Fx, Spine x-ray, VFA
Bone Mineral Density
No Fragility Fractures
FRAX 10 Year Risk
T-Score: –1.0 to –2.4 and Drug Naïve
Hip, Vertebral, Wrist, Humerus
T-Score ≤–2.5
Hip Fracture ≥3%
Major Osteoporotic Fracture ≥20%
Lifestyle Measures
Adequate Calcium Intake
Adequate Vitamin D Intake
Regular Exercise
OSTEOPOROSIS
Evaluate
Secondary +/or Contributing Factors
Medication Choice: Fracture Risk Stratification
Low / Moderate Risk
High Risk
Old Age
Prior Fracture
BMD Very Low
Fall Risk High
Steroid Use
Oral Bisphosphonate
Zoledronic Acid
Denosumab
Zoledronic Acid
Denosumab
Teriparatide
Abaloparatide

Fig. 15.3 Suggested Osteoporosis Diagnosis and Management Algorithm. High Risk Patients: old age, prior fracture, very low BMD, high fall risk, glucocorticoid use.

KEY POINTS

1. Nonpharmacological measures that are effective for prevention/treatment of osteoporosis include adequate calcium and vitamin D nutrition, regular exercise, fall prevention, smoking cessation, and limitation of alcohol and caffeine intake.
2. Pharmacological therapy should be initiated in patients who have had a fragility fracture, a BMD T-score ≤-2.5, or a FRAX-derived 10-year risk of ≥3% for hip fractures and ≥20% for other major osteoporosis fractures.
3. The two primary categories of effective medications for treating osteoporosis are antiresorptive agents and anabolic agents.
4. Osteonecrosis of the jaw and atypical femoral fractures have been reported in some patients using antiresorptive medications but not anabolic medications.
5. BMD loss during osteoporosis therapy is most often due to therapy nonadherence, but affected patients should also be investigated for other causes of bone loss.
6. Bisphosphonates and teriparatide improve BMD and reduce fractures in patients with glucocorticoid-induced osteoporosis.

TOP SECRETS

Medical therapy for osteoporosis should be offered to any patient who has had a fragility fracture, who has a bone mineral density T-score ≤-2.5, or a FRAX 10-year risk of ≥3% for a hip fracture or ≥20% for any major osteoporosis fracture.

The greatest bone mineral density gains result from sequential therapy starting first with an osteoanabolic agent followed by treatment with an antiresorptive medication.

Rapid bone loss and multiple vertebral fractures associated with accelerated bone resorption have been reported after discontinuation of Denosumab (Prolia).

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) are uncommon complications that can result from the use of antiresorptive agents, but these complications do not occur with osteoanabolic agents.

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CHAPTER 16

Osteomalacia, Rickets, and Vitamin D Insufficiency

William Edgar Duncan

1. Why are osteomalacia and rickets important?

In the United States at the beginning of the 20th century, rickets caused by a deficiency of vitamin D was common in urban areas. In the 1920s, rickets was virtually eliminated by an understanding of the antirachitic properties of sunlight and the use of cod liver oil (which contains large amounts of vitamin D). However, with the subsequent development of effective treatments for previously fatal diseases that adversely affect vitamin D metabolism (such as chronic renal failure) and with a greater understanding of both vitamin D and mineral metabolism, many additional clinical conditions associated with osteomalacia or rickets have been recognized. Today, undiagnosed vitamin D deficiency or insufficiency is seen in 23% of the US population. Inadequate vitamin D is found more commonly in non-Hispanic blacks and Mexican Americans, and in women of all races and ethnicities. Thus, for individuals with osteoporosis or fracture, inadequate vitamin D may be an unsuspected contributor to their bone loss.

2. What are osteomalacia and rickets?

Osteomalacia and *rickets* are terms that describe the clinical, histologic, and radiologic abnormalities of bone that are associated with more than 50 diseases and conditions. Osteomalacia occurs in mature (adult) bone, whereas rickets is a disorder of growing bone. Although rickets and osteomalacia were initially viewed as distinct clinical entities, the same pathologic processes may result in either disorder. In both conditions, mineralization of newly formed osteoid (the bone protein matrix) is inadequate or delayed. In rickets, there is also defective chondrocyte differentiation and defective mineralization in both bones and cartilage of the epiphyseal growth plates, which results in growth retardation and skeletal deformities not typically seen in adults with osteomalacia.

3. Describe how vitamin D is synthesized and metabolized.

Serum vitamin D comes from two sources: dietary intake and conversion by ultraviolet (UV) irradiation of 7-dehydrocholesterol or ergosterol in the skin. Vitamin D is then transported to the liver, where it is converted to 25-hydroxyvitamin D (25OHD) by the 25-hydroxylase enzyme. In the kidney, 25OHD is converted to the active hormone, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$), by 1-α-hydroxylase. This active vitamin D metabolite acts in many tissues, including the intestine (to increase calcium absorption), the kidney (to increase calcium reabsorption), the parathyroid glands (to decrease PTH secretion), and bone (to stimulate osteoblast maturation and bone matrix synthesis). $1,25(OH)_2D$ and 25OHD are inactivated by cytochrome P450 CYP24A1 in the kidney and by cytochrome P450 3A4 in the liver (Fig. 16.1). Even when dietary intake and UV-mediated vitamin D synthesis are normal, vitamin D deficiency may still occur in association with severe malabsorptive, renal, or liver disease. Beside its role in mineralization of bone and calcium homeostasis, observational studies have suggested that vitamin D may also play a role in cardiovascular and neurological diseases, insulin resistance and diabetes, malignancies, autoimmune conditions, and infectious diseases. We await the results of randomized controlled trials to better understand the extraskeletal actions of vitamin D in health and disease.

4. List the causes of osteomalacia and rickets.

The primary abnormality of bone in patients with either osteomalacia or rickets is undermineralization of the bone matrix. The major mineral in bone is hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$). Any disease that results in decreased availability to bone of either calcium or phosphorus may result in osteomalacia or rickets (Table 16.1). Therefore causes of osteomalacia and rickets fall into three categories: (1) low calcium intake in children or disorders associated with abnormalities of vitamin D metabolism or action that limit the availability of calcium for mineralization of bone;

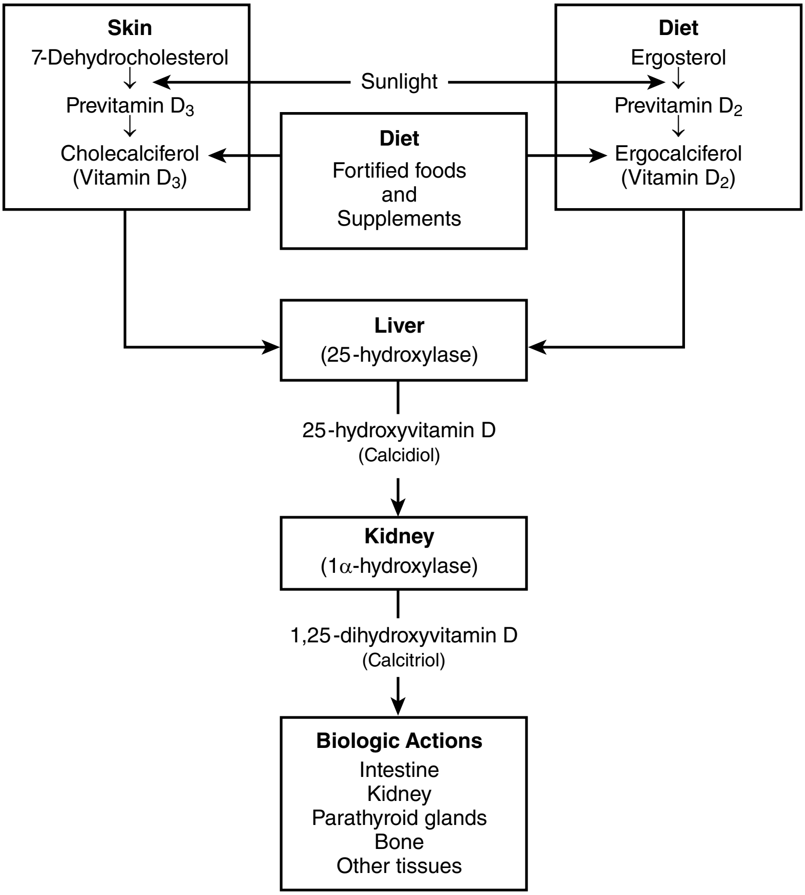
Skin
7-Dehydrocholesterol
Previtamin D3
Cholecalciferol
(Vitamin D3)
Sunlight
Diet
Ergosterol
Previtamin D2
Ergocalciferol
(Vitamin D2)
Diet
Fortified foods
and
Supplements
Liver
(25-hydroxylase)
25-hydroxyvitamin D
(Calcidiol)
Kidney
(1α-hydroxylase)
1,25-dihydroxyvitamin D
(Calcitriol)
Biologic Actions
Intestine
Kidney
Parathyroid glands
Bone
Other tissues

Fig. 16.1 Synthesis, metabolism, and sites of action of vitamin D.

(2) disorders associated with abnormalities of phosphorus metabolism; and (3) a small group of disorders in which vitamin D and mineral metabolism is normal.

5. Discuss the disease processes that interfere with the metabolism of vitamin D.

Clinically apparent vitamin D deficiency is rarely seen in the United States except when exposure to sunlight and intake of vitamin D–fortified milk and other dairy products is limited. However, many elderly Americans are at risk for occult vitamin D deficiency or insufficiency because of sun avoidance, the use of sunscreens, and an age-related decrease in the dermal synthesis of vitamin D, impaired hepatic and renal hydroxylation of vitamin D, and diminished intestinal responsiveness to 1,25$(OH)_2$D. Celiac disease or sprue, regional enteritis, intestinal bypass surgery, partial gastrectomy, chronic liver disease, primary biliary cirrhosis, pancreatic insufficiency, certain medications, and chronic renal failure have also been associated with the development of osteomalacia.

6. List genetic disorders that interfere with vitamin D synthesis or action.

The term *vitamin D–dependent rickets* (VDDR) describes a group of extremely rare hereditary disorders that are characterized by early-onset rickets due to the inability to maintain adequate concentrations of the active forms of vitamin D (VDDR type I and type III) or to adequately respond to 1,25$(OH)_2$D (VDDR type II). VDDR type I is caused by inactivating mutations of either the renal 1α-hydroxylase (VDDR type Ia) or the liver 25-hydroxylase gene (VDDR type Ib). VDDR type II is caused by a mutation of the vitamin D receptor (VDR) gene or the presence of a protein that interferes with the VDR-DNA interaction. VDDR type III is caused

TABLE 16.1 Conditions Associated With Osteomalacia and Rickets

CONDITION	PRIMARY MECHANISM*
Abnormal vitamin D metabolism or action	
Nutritional deficiency	Vitamin D deficiency
Malabsorption	Malabsorption of vitamin D
Primary biliary cirrhosis	Malabsorption of vitamin D
Chronic renal disease	Impaired 1α-hydroxylation of 25OHD
Chronic liver disease	Impaired 25-hydroxylation of vitamin D
VDDR type Ia	1α-hydroxylase deficiency
VDDR type Ib	25-hydroxylase deficiency
VDDR type II	Impaired vitamin D receptor function
VDDR type III	Inactivation of vitamin D metabolites
Drugs (phenytoin, barbiturates, cholestyramine)	Increased catabolism and/or excretion of vitamin D
Phosphate deficiency or renal phosphate wasting	
Diminished phosphate intake	Phosphate deficiency
Excessive aluminum hydroxide intake	Increased binding of intestinal phosphate
Inherited hypophosphatemic rickets	Genetic mutations causing phosphate wasting
Tumor-induced osteomalacia	Urinary phosphate wasting caused by FGF23
Miscellaneous renal tubular defects	Renal phosphate transport defect (RTA, FS)
Normal vitamin D and phosphate metabolism	
Hypophosphatasia	Alkaline phosphatase deficiency
Drugs (fluoride, aluminum)	Inhibition of mineralization or stimulation of matrix synthesis
Osteogenesis imperfecta	Abnormal bone collagen
Fibrogenesis imperfecta ossium	Defective bone matrix

*Other causes may also may contribute to bone disease.
25OHD, 25-hydroxyvitamin D; *VDDR*, vitamin D dependent rickets; *FGF23*, Fibroblast Growth Factor 23; *RTA*, = renal tubular acidosis; *FS*, Fanconi syndrome.

by a gain-of-function mutation of the cytochrome P450 liver enzyme CYP3A4 that converts $1,25(OH)_2D$ to an inactive metabolite (Fig. 16.1).

7. Describe the regulation of serum phosphorus.

Serum phosphorus is regulated by the coordinated action of $1,25(OH)_2D$, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23). Phosphorus concentrations are increased by $1,25(OH)_2D$, which enhances intestinal phosphate absorption. PTH lowers serum phosphorus by promoting renal phosphate excretion. FGF23 also lowers serum phosphate by forming a complex with the FGF23 receptor and the Klotho protein to enhance renal phosphate excretion by down-regulating renal sodium-phosphate transporters. FGF23 also reduces intestinal phosphate absorption by lowering serum $1,25(OH)_2D$ through inhibition of the renal 1-α-hydroxylase enzyme and stimulation of renal 24-hydroxylase.

8. What abnormalities of phosphate metabolism result in osteomalacia or rickets?

Nutritional phosphate deficiency, decreased intestinal absorption of phosphate due to ingestion of phosphate binders (e.g., aluminum hydroxide), or renal phosphate wasting may result in osteomalacia or rickets. The most common genetic phosphate wasting syndromes are X-linked hypophosphatemic rickets (XLH) and autosomal dominant hypophosphatemic rickets (ADH). XLH and ADH have similar clinical and biochemical findings except that XLH displays male to male transmission. XLH is caused by mutations in the PHEX gene and ADH by mutations of FGF23 that make it resistant to cleavage. Both mutations result in an increased circulating FGF23 bioactivity, renal phosphate wasting, and rickets. Tumor-induced osteomalacia (also called oncogenic osteomalacia) is a nonhereditary phosphate wasting syndrome caused by neoplasms of mesenchymal origin which secret FGF23.

9. How does chronic renal failure cause osteomalacia and rickets?

Chronic renal failure is associated with a number of bone diseases collectively referred to as renal osteodystrophy: osteomalacia or rickets, adynamic bone, osteitis fibrosa cystica (due to long-standing secondary hyperparathyroidism), and a combination of both osteomalacia and osteitis fibrosa cystica (termed *mixed renal osteodystrophy*). Rickets or osteomalacia is usually a late finding in the course of the kidney disease and is rarely seen before patients begin dialysis. Rickets or osteomalacia associated with chronic renal failure is caused by decreased circulating concentrations of 1,25$(OH)_2$D, by aluminum intoxication from aluminum-containing antacids used as phosphate binders or an aluminum-contaminated dialysate, and possibly by the chronic metabolic acidosis associated with the renal failure.

10. What are the signs and symptoms associated with osteomalacia?

In adults, osteomalacia may be asymptomatic. When symptomatic, osteomalacia may present with diffuse skeletal pain (often aggravated by physical activity or palpation of bone), muscle weakness, and sometimes muscle wasting. The muscle weakness often involves the proximal muscles of the lower extremities and may result in a waddling gait and difficulties rising from a chair or climbing stairs. The bone pain is described as dull and aching and is usually located in the back, hips, knees, legs, and at sites of fractures. In patients with osteomalacia, fractures may result from minor trauma.

11. Describe the clinical findings of rickets.

Because of the impaired calcification of cartilage at the growth plates in children with rickets, the clinical manifestations of rickets differ significantly from those of osteomalacia. Widening of the metaphyses (the growth zones between the epiphysis and diaphysis), slowed growth, and various skeletal deformities are prominent in rickets. The effects of rickets are greatest at sites where the growth of bone is most rapid. Because the rate of skeletal growth varies with age, the manifestations of rickets also vary. One of the earliest signs of rickets in infants is craniotabes (abnormal softness of the skull). In older infants and younger children, thickening of the forearm at the wrist and swelling of the costochondral junctions (also known as the rachitic rosary) and Harrison's groove (a lateral indentation of the chest wall at the site of attachment of the diaphragm) may be present. In older children, bowing of the tibia and fibula may be observed. At any age, if rickets (or osteomalacia) is associated with hypocalcemia, paresthesias of the hands and around the mouth, muscle cramps, positive Chvostek's and Trousseau's signs, tetany, and seizures may be present.

12. What biochemical abnormalities are seen with osteomalacia and rickets caused by vitamin D deficiency?

The laboratory abnormalities associated with osteomalacia or rickets depend on the underlying defect or process causing the bone disease. To understand the biochemical abnormalities observed in conditions associated with the abnormal metabolism of vitamin D, an understanding of the body's response to hypocalcemia and knowledge of the vitamin D metabolic pathway are necessary. Thus, in patients with nutritional vitamin D deficiency or malabsorption, the low vitamin D concentrations result in a low or low-normal serum calcium concentration, which serves as a stimulus for increased secretion of parathyroid hormone (causing secondary hyperparathyroidism). This secondary hyperparathyroidism, in turn, causes increased renal excretion of phosphate, decreased serum phosphate, elevated alkaline phosphatase concentrations, and reduced urinary calcium excretion.

13. What are the vitamin D metabolite concentrations associated with the diseases that interfere with vitamin D metabolism or action?

Depending on the abnormality of vitamin D metabolism, different vitamin D metabolite patterns may be observed. In nutritional vitamin D deficiency, the 25OHD and 1,25$(OH)_2$D concentrations are low. In VDDR type Ia (caused by deficiency of the renal 1α-hydroxylase enzyme), normal or increased serum 25OHD and low or undetectable serum $1,25(OH)_2D$ concentrations are observed. In VDDR type Ib (caused by lack of hepatic 25-hydroxylase), 25OHD and $1,25(OH)_2D$ are decreased. In contrast, in VDDR type II (caused by resistance of target organs to $1,25[OH]_2D$), the concentrations of both 25OHD and $1,25(OH)_2D$ are elevated and in VDDR type III (caused by accelerated catabolism of vitamin D metabolites) 25OHD and $1,25(OH)_2D$ are decreased.

14. What radiographic findings are associated with osteomalacia and rickets?

The biochemical abnormalities associated with rickets and osteomalacia are usually evident before radiographic abnormalities are observed. The most common radiographic change in patients with osteomalacia is a reduction in bone mass. Pseudofractures (also called Looser zones or Milkman fractures) or complete fractures may also be observed. Pseudofractures are transverse radiolucent bands ranging from a few millimeters to several centimeters in length, usually perpendicular to the surface of the bones. They are most often bilateral and are particularly common in the femur, pelvis, and small bones of the hands and feet.

Certain radiographic abnormalities are primarily observed in children with rickets. These include fraying of the metaphyses of the long bones, widening of the unmineralized epiphyseal growth plates, and bowing of the legs. The skeletal deformities observed in children with rickets may persist into adulthood. Patients with osteomalacia may also have additional radiographic findings as a result of secondary hyperparathyroidism. Such findings include subperiosteal resorption of the phalanges, loss of the lamina dura of the teeth, widening of the spaces at the symphysis pubis and sacroiliac joints, and presence of brown tumors or bone cysts.

15. Discuss the histologic features of osteomalacia.

The two diagnostic histologic findings of osteomalacia are the presence of widened osteoid seams and increased mineralization lag time (the time necessary for newly deposited matrix to mineralize). The mineralization lag time is assessed by administration of two short courses of oral tetracycline several weeks apart before a bone biopsy. Because tetracycline is deposited at the mineralization front in newly formed bone, the lag time may be determined by measuring the distance between the two fluorescent tetracycline bands in the biopsied bone. Depending on the cause of the osteomalacia, hyperparathyroid bone changes may also be seen. Because of the many clinical signs and symptoms, radiographic findings, and biochemical abnormalities associated with osteomalacia or rickets, none of these tests or findings are diagnostic. The bone biopsy remains the gold standard in establishing the diagnosis of rickets and osteomalacia. The evaluation of a bone biopsy must be performed by personnel trained in the interpretation of bone histology.

16. Describe the therapy for osteomalacia and rickets caused by vitamin D deficiency.

The goal of therapy for patients with osteomalacia and rickets caused by an abnormality of vitamin D metabolism is to correct the hypocalcemia and the deficiency of active vitamin D metabolites by administration of calcium salts (as supplements or via diet) and vitamin D preparations. In the United States, vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), 25OHD (calcifediol), $1,25(OH)_2D$ (calcitriol), and vitamin D analogues are available. Each of these preparations has a different half-life and potency. The choice and dose of vitamin D preparation are determined by the underlying pathologic defect of vitamin D metabolism. For patients with nutritional vitamin D deficiency, treatment with physiologic doses of vitamin D_2 or D_3 along with elemental calcium is often sufficient to heal the osteomalacia. Osteomalacia due to hepatobiliary disease or chronic renal failure is managed with calcitriol or one of its analogs.

17. What are the treatments for osteomalacia and rickets not caused by vitamin D deficiency?

VDDR type 1a is treated with physiologic doses of calcitriol, whereas VDDR type 1b is treated with physiologic doses of 25OHD. In contrast, therapy for VDDR type II consists of administration of calcitriol in doses up to 60 mcg/day (an extraordinarily high dose), along with large doses of oral calcium or calcium infusions to heal the rickets in these patients. Hypophosphatemic rickets (XLH and ADH) is treated with oral phosphorus administered three to five times daily with calcitriol. This treatment leads to resolution of radiographic rickets and improved but not normal growth. For conditions associated with increased bioactivity of FGF23 (e.g., most XLH, ADH and tumoral osteomalacia), a monoclonal antibody that binds FGF23 (Burosumab) successfully lowers circulating FGF23 and normalizes serum phosphorus and improves bone mineralization. Tumor removal or irradiation is required for definitive treatment of tumor-induced osteomalacia. In chronic renal failure with aluminum-induced osteomalacia, aluminum is removed from the affected bone by treatment with the chelating agent deferoxamine. The bone disease can then be treated with calcium and calcitriol. Osteomalacia associated with renal tubular acidosis is treated with bicarbonate to correct the acidosis and vitamin D.

18. How is vitamin D insufficiency diagnosed and why is it important?

The most stable and plentiful circulating metabolite of vitamin D, 25OHD, has a half-life of about 3 weeks, making it the most suitable indicator of nutritional vitamin D status. A global consensus conference has defined normal vitamin D status (based on 25OHD concentrations) as > 50 nmol/L (20 ng/ml), insufficient vitamin D as 30 to 50 nmol/L (12 to 20 ng/ml), and vitamin D deficiency as < 30 nmol/L (12 ng/ml). The Nutrition Examination Survey in 2014 found that 5% of the population of the United States 1 year or older had 25OHD concentrations less than 12 ng/ml and 18% had 25OHD concentrations between 12 and 19 ng/ml. As circulating 25OHD concentrations decrease from the normal range, there is an increasing negative impact on skeletal health, and therefore vitamin D insufficiency should be treated with supplemental vitamin D.

19. What are the complications of treatment with vitamin D preparations?

When high doses of vitamin D or one of the more potent vitamin D metabolites are used, it is important to carefully monitor for hypercalcemia. Mild hypercalcemia may be asymptomatic. However, severely hypercalcemic patients may complain of anorexia, nausea, vomiting, weight loss, headache, constipation, polyuria, polydipsia, and altered mental status. Impaired renal function, nephrocalcinosis, nephrolithiasis, and even death may eventually ensue. If vitamin D intoxication occurs, all calcium supplements and vitamin D preparations must be discontinued immediately and therapy for hypercalcemia instituted.

KEY POINTS

- Osteomalacia and rickets are disorders that cause inadequate or delayed mineralization of bone.
- Osteomalacia occurs in mature (adult) bone, whereas rickets occurs in growing bone. While the causes of these two conditions may be the same, the clinical and radiographic findings differ.
- The causes of osteomalacia and rickets fall into three categories: (a) low calcium intake in children or disorders associated with abnormal vitamin D metabolism or action; (b) disorders associated with abnormal phosphate metabolism; and (c) a small group of disorders with normal vitamin D and mineral metabolism.
- Vitamin D insufficiency is common in the United States and has a negative impact on skeletal health.

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CHAPTER 17

Paget's Disease of Bone

Christine M. Swanson

1. What is Paget's disease of bone (PDB)?

PDB is a chronic disease characterized by abnormal bone remodeling in one or more bones. Pagetic osteoclasts (bone cells responsible for bone resorption) are abnormally large and overactive causing focal areas of excessive bone resorption. Compensatory increases in bone formation (by osteoblasts) at pagetic sites result in disorganized, structurally weaker bone that is often increased in size. Sir James Paget first described this condition in 1876 and referred to it as osteitis deformans, but there is evidence that the condition existed in Western Europe during the Roman period. PDB can lead to bone pain, skeletal deformities, pseudofractures, and osteoarthritis, though many people with PDB are asymptomatic at diagnosis.

2. What causes Paget's disease of bone?

The cause of PDB is unknown and may have genetic and environmental influences. Mutations in the *SQSTM1* gene, which encodes a protein that plays a role in osteoclast function, are seen in 40–50% of familial cases of PDB. Paramyxovirus infection has been proposed as a potential trigger for PDB, as pagetic osteoclasts have been found to contain intranuclear structures resembling paramyxovirus nucleocapsids, though no virus has been cultured from pagetic osteoclasts. The incidence and severity of PDB are decreasing worldwide, and this may reflect changes in environmental contributions to PDB.

3. How does Paget's disease of bone typically present?

PDB is typically diagnosed when elevated alkaline phosphatase (ALP) or an abnormal radiograph (x-ray) is found incidentally in patients being evaluated for other reasons. Symptoms depend on the site and extent of involvement. Thirty to forty percent of patients are symptomatic at diagnosis with the most common symptom being bone pain. Frequently, bone pain develops later in the disease course—it is characterized as a deep and aching pain that occurs with rest or activity and is often worse at night.

4. Who is typically affected by Paget's disease of bone?

PDB prevalence increases with age. It typically affects older adults and is uncommon before the age of 40. Incidence of PDB also varies based on geography and sex. Men appear to be more commonly affected than women. PDB most commonly affects those of European descent and less commonly those of African and Asian descent. In the United States, PDB is estimated to affect 2–3% of the adult population over the age of 55.

5. How is Paget's disease of bone diagnosed?

PDB is a radiographic diagnosis and can be made with plain x-ray. Typical findings of PDB on radiograph include focal osteolysis with sclerotic changes, thickening of the cortex, coarse trabecular pattern, and bone enlargement (Fig. 17.1). ALP should be measured, which is often, though not always, elevated.

6. What is the differential diagnosis of Paget's disease of bone?

The differential for radiographic PDB may include chronic osteomyelitis, vertebral hemangioma, fibrous dysplasia, metastatic disease, metaphyseal dysplasia (Engelmann disease), hyperostosis frontalis interna, familial expansile osteolysis, sternocostal clavicular hyperostosis, osteosarcoma and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis). Elevated ALP can be seen in liver or biliary disease or any condition with increased bone turnover (e.g., osteomalacia, hyperparathyroidism, skeletal metastases).

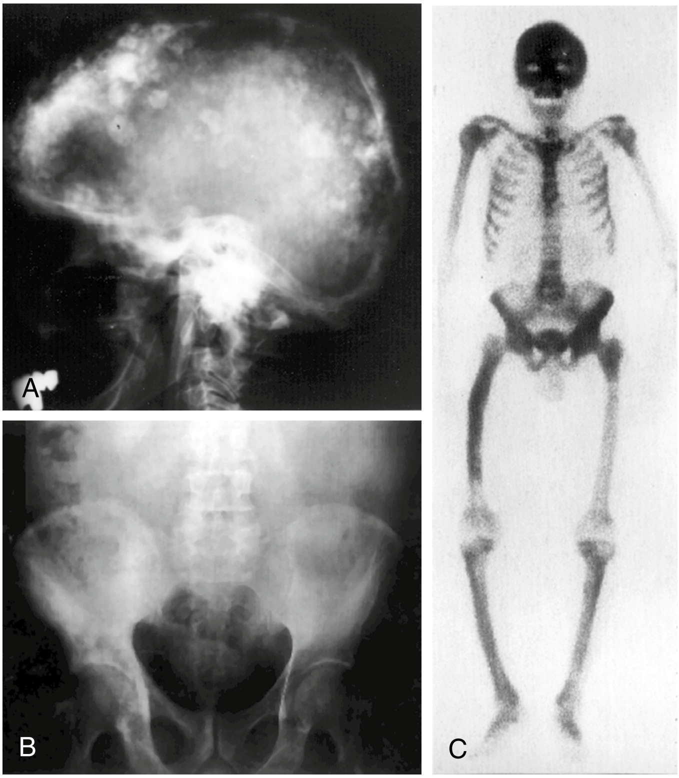

Fig. 17.1 The characteristic radiographic and scintigraphic findings seen in Paget's disease of bone. (**A**) A skull radiograph showing a thickened cranium with regions of dense sclerosis and osteopenia resulting in a "cotton wool" appearance. (**B**) A pelvic radiograph showing right hemipelvic loss of normal trabeculation, sclerosis, and cortical thickening, along with sclerosis of the iliopectineal line. (**C**) Full-body scintigraphy showing increased uptake in the skull, pelvis, lumbar spine, bilateral femurs with bowing of the right, tibias, scapula, and bilateral proximal humerus.

7. Which bones are involved in Paget's disease of bone?

PDB may be monostotic (involvement of one bone), or more commonly polyostotic (involvement of ≥2 bones). It has a predilection for the axial skeletal but can affect nearly any bone in the body. The most frequently involved bones are the pelvis (70%), femur (55%), lumbar spine (53%), skull (42%), and tibia (32%). Each individual pagetic site may progress or evolve over time; however, the number of skeletal sites involved is usually stable over time, and it is rare for new skeletal lesions to develop after diagnosis.

8. What are the typical histological and radiological appearances and triphasic progression of pagetic bone lesions?

PDB progresses through three phases. First, there is a focal increase in bone resorption due to increased osteoclast activity by numerous enlarged, often multinucleated osteoclasts. Radiographic findings include bone loss, wedge-shaped areas of resorption in long bones, and circumscribed lytic lesions in the skull (osteoporosis circumscripta). Second, increased osteoblast activity and accelerated bone formation occur, resulting in disorganized collagen architecture (mosaic or woven, instead of the normal lamellar pattern) and a mixed lytic/sclerotic phase. This abnormal bone has impaired strength and is at higher risk for fracture. On x-ray, bones are enlarged and sclerotic; bowing deformities, transverse linear radiolucencies ("pseudofractures"), and thickening of the calvarium may be seen. Finally, there is reduced bone cell activity, and persistence of abnormal bone architecture including enlarged, sclerotic bones.

TABLE 17.1 Bisphosphonates Used in the Treatment of Paget's Disease of Bone

DRUG NAME	DOSAGE	DURATION
Zoledronate	5 mg IV once	Not Applicable
Alendronate	40 mg per day by mouth	6 months
Risedronate	30 mg per day by mouth	2 months

IV, intravenous

9. Which laboratory tests should be obtained to evaluate and monitor Paget's disease of bone?

ALP, calcium, albumin, liver function tests, and 25-hydroxyvitamin D should be obtained in patients with suspected or known PDB. ALP can be within normal limits in those with limited, monostotic disease or during the initial osteolytic phase of PDB, but rises during the osteoblastic phase and can correlate with disease activity. Measurement of ALP is the preferred assay in PDB. If liver disease is present or the ALP is normal, other markers of bone formation such as bone-specific alkaline phosphatase (BSAP) or procollagen type I N-terminal propeptide (P1NP) can be checked. The elevated turnover marker can be followed over time every 6–12 months to assess a patient's response to treatment and/or PDB activity.

10. What imaging is recommended to determine the extent of skeletal involvement in Paget's disease of bone and for monitoring?

Plain x-rays are used to diagnose PDB, but the extent of PDB involvement is best measured by radionuclide bone scan. Bone scan findings are nonspecific (e.g., may see false positives at osteoarthritic sites), but it is the most sensitive exam for identifying PDB lesions. Early symptomatic lesions may be apparent on bone scan before x-ray, whereas burned-out pagetic lesions that are easily seen on x-ray may not have increased uptake on bone scan. It is recommended that newly diagnosed Paget's patients have a bone scan during their initial evaluation, followed by x-rays of involved sites. CT, MRI, and PET imaging are not routinely used in PDB.

11. What medications are available to treat Paget's disease of bone?

Adequate calcium and vitamin D are essential in PDB. Nitrogen containing bisphosphonates (Table 17.1) are considered first-line therapy for the treatment of PDB, as they target affected sites and effectively suppress bone resorption. These medications include intravenous (zoledronate, pamidronate) and oral formulations (alendronate, risedronate). Calcitonin is less effective and not commonly used. There are case reports of denosumab being used in treatment of PDB; however, PDB is not an approved indication for denosumab. Additionally, there are significant risks with stopping denosumab without subsequent antiresorptive therapy (declining bone mineral density, increased risk of multiple vertebral compression fractures) (see *Anastasilakis et al., Journal of Clinical Medicine 2021*).

12. Which pharmacological agent is the treatment of choice for Paget's disease of bone?

Zoledronate, an intravenous infusion, is the treatment of choice for PDB because it has the fastest, most dramatic, and sustained effect on ALP and symptoms (pain, quality of life). After a single dose, 96% of patients normalize or have at least a 75% reduction in ALP levels at 6 months. Zoledronate is effective even in PDB patients who did not respond to previous treatment with other bisphosphonates. Sustained biochemical response to zoledronate may last for 6 years. Bisphosphonates are contraindicated in those with a CrCl <35 mL/min.

13. What are the indications for treatment of Paget's disease of bone?

Bisphosphonate treatment should be considered for:

- Symptoms (including bone pain that corresponds to a site of metabolically active PDB). Bisphosphonate therapy may help clarify if pain is due to bone or osteoarthritic pain.
- Those at high risk of developing complications from PDB lesion (e.g., fracture in weight bearing bones, headaches or nerve compression from involvement of the skull or spine, disease near major joints, hearing loss).

- Prior to orthopedic or elective surgery at or near a pagetic site to reduce hypervascularity and perioperative blood loss.
- Hypercalcemia in the setting of immobilization

14. What are the treatment goals in Paget's disease?

Response to therapy is typically assessed with bone turnover markers. The preferred marker, ALP, normally decreases 1–2 weeks after zoledronate, reaching a nadir by 3–6 months. Bone resorption markers (e.g., CTx, urinary NTx) fall more rapidly after treatment but are more expensive. Other bone formation markers (e.g., P1NP, BSAP) may be trended if ALP cannot be used (e.g., liver disease). Sustained remission may be indicated by bone turnover markers in the lower half of the reference range, and retreatment may be considered if pagetic symptoms recur or bone turnover markers become elevated. There are no data to support that ALP normalization decreases risk of long-term complications, although trials have been limited in size and duration.

15. What are the side effects of pharmacological therapy?

Bisphosphonates have been associated with a small increased risk of osteonecrosis of the jaw (particularly with invasive dental procedures and in cancer patients) and atypical (subtrochanteric) femoral fractures. Bisphosphonates can be nephrotoxic and are contraindicated in patients with impaired renal function (CrCl <35 mL/min). Hypocalcemia can occur with bisphosphonate treatment, especially in those patients with vitamin D deficiency. Different formulations have specific side effects that should be considered such as an acute phase response (IV) and esophagitis/dyspepsia (oral). The acute phase response may be more severe in PDB patients than when used for osteoporosis because of greater osteoclast activity. Optimizing vitamin D status prior to zoledronate infusion may decrease the risk of an acute phase reaction in patients with PDB.

16. What complications can arise in Paget's disease of bone?

Osteoarthritis, bone deformity, fracture, pseudofracture, and bone enlargement can be signs of long-standing PDB. Hearing loss can occur in patients with skull involvement and may be due to cochlear damage from bony overgrowth. Other neurologic deficits due to impingement include spinal stenosis and radiculopathy. Obstructive hydrocephalus can occur if there is compression at the base of the skull. Pseudofractures are a characteristic finding in PDB and can progress to complete fractures. High-output cardiac failure (particularly in polyostotic disease) and hypercalcemia (when immobilized) are rarer complications of PDB. PDB lesions can rarely transform into giant cell tumor (usually a benign condition) or osteosarcoma.

17. What is the risk of osteosarcoma in a patient with Paget's disease of bone?

Transformation of a pagetic site to osteosarcoma has a poor prognosis but is quite rare, occurring in <1% of patients. Osteosarcoma should be suspected in PDB patients with increased bone pain and swelling, new mass, or new fracture at a pagetic site. MRI is useful in these instances to distinguish pagetic bone lesions from malignancies.

KEY POINTS

- Paget's disease of bone (PDB) is a chronic condition characterized by focal areas of abnormal osteoclasts that cause excessive bone resorption, followed by abnormal bone formation resulting in disorganized, weak bone.
- PDB commonly presents as an incidental discovery of elevated ALP, or bone abnormality on a nonrelated imaging study.
- X-rays are used to diagnose PDB and nuclear medicine bone scans to evaluate extent of disease.
- The treatment of choice of PDB is IV zoledronate, and treatment is indicated in PDB patients with symptoms (e.g., bone pain), hypercalcemia, and those at high risk of developing complications from PDB or undergoing surgery at or near a pagetic site.

WEBSITE

https://www.bonehealthandosteoporosis.org/pagets/

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Hypercalcemia

Leonard R. Sanders

CHAPTER 18

1. What is hypercalcemia, and how does protein binding affect the calcium level?

Hypercalcemia is a corrected total serum calcium value above the upper limit of the normal range or an elevated ionized calcium value. Calcium is 50% free (ionized), 40% protein-bound, and 10% complexed to phosphate, citrate, bicarbonate, sulfate, and lactate. Only free calcium changes cause symptoms and signs. Of the protein-bound calcium, about 80% is bound to albumin and 20% to globulins. A decrease or increase in serum albumin of 1 g/dL from 4 g/dL decreases or increases the serum calcium by 0.8 mg/dL. An increase or decrease in serum globulin by 1 g/dL increases or decreases serum calcium by 0.16 mg/dL. Such protein changes do not affect free calcium or cause calcium-related symptoms.

2. How common is hypercalcemia and its main associated conditions?

Hypercalcemia affects 0.5% to 1% of the general population. The incidence may increase to 3% among postmenopausal women. Primary hyperparathyroidism (PHPT) causes 70% of outpatient cases and 20% of inpatient cases of hypercalcemia. Cancer causes most inpatient hypercalcemia. About 10% to 30% of patients with malignancy experience hypercalcemia. Hyperparathyroidism and cancer cause 90% of all hypercalcemia. About 10% to 20% of patients with hyperparathyroidism experience nephrolithiasis. Calcium oxalate stones are usually the most common, but calcium phosphate stones are more characteristic.

3. How would you classify mild, moderate, and severe hypercalcemia?

First, consider the patient's general health, hypercalcemic symptoms, and the reference range for your lab, which is often 8.5 to 10.5 mg/dL. Then, correct the calcium for the albumin concentration as follows.

$$\text{The corrected calcium} = \text{calcium measured} + [(4.0\text{-albumin}) \times 0.8]$$

Corrected calcium levels above the reference range of your lab define hypercalcemia. Mild hypercalcemia occurs when calcium levels are below 12 mg/dL, moderate hypercalcemia is between 12 and 14 mg/dL, and severe hypercalcemia is above 14 mg/dL.

4. What are the signs and symptoms of hypercalcemia?

No symptoms are typically present in cases of mild hypercalcemia (<12 mg/dL). Moderate or severe hypercalcemia, as well as rapidly developing mild hypercalcemia, may cause symptoms and signs. Symptoms and signs involve:

- The central nervous system (confusion, lethargy, thirst, stupor, coma, psychosis).
- The gastrointestinal tract (anorexia, nausea, constipation, acid peptic disease, pancreatitis).
- The kidneys (polyuria, nephrolithiasis, nephrocalcinosis, kidney injury).
- The musculoskeletal system (arthralgias, myalgias, weakness).
- The vascular system (hypertension).

A short QT interval is the classic electrocardiography (ECG) change associated with hypercalcemia. Severe hypercalcemia can cause dysrhythmias, sinus arrest, disturbances in atrioventricular (AV) conduction, J waves (Osborn waves), and ST-segment elevation mimicking myocardial infarction.

5. What are the primary sources of serum calcium?

Bone calcium is approximately 1 kg, comprising 99% of the body's calcium. The body maintains normal serum calcium levels by regulating calcium absorption, resorption, and reabsorption. These processes occur, respectively, in the gut, bone, and kidney. Of 1000 mg/day of dietary calcium intake, the gut absorbs 300 mg/day, secretes 100 mg/day, and excretes 800 mg/day. Net

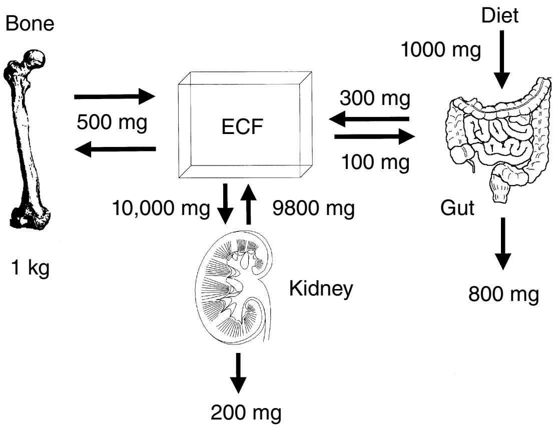

Fig. 18.1 Normal calcium balance. ECF, Extracellular fluid.

absorption averages 200 mg/day. Calcium absorption is usually about 30% of dietary calcium; however, absorption may increase to >50% when people take large doses of calcitriol. The kidney reabsorbs 98% of filtered calcium and excretes 200 mg/day. Bone exchanges about 500 mg of calcium daily with serum (Fig. 18.1).

6. What are the major anatomic and physiologic determinants of vitamin D?

Diet, skin, liver, and kidney control the amount, synthesis, and secretion of vitamin D. Dietary sources of vitamin D include liver, fish oils, egg yolks, vitamin D–fortified foods, and vitamin D supplements. Skin exposure to ultraviolet sunlight activates 7-dehydrocholesterol to previtamin D, which subsequently rearranges to form vitamin D_3 (cholecalciferol). Hepatic 25-hydroxylase then converts vitamin D to 25-hydroxyvitamin D (25OHD) or calcifediol. 25-OH vitamin D circulates and interacts with two renal mitochondrial hydroxylases. High parathyroid hormone (PTH), low phosphate, and low calcium levels stimulate 1-alpha-hydroxylase activity to increase conversion of 25OHD to 1,25$(OH)_2$ vitamin D (calcitriol)—the most potent metabolite of vitamin D. Low PTH, high phosphate, and high calcium levels suppress 1-alpha-hydroxylase activity and stimulate 24-hydroxylase activity. This process inhibits calcitriol production and, through 24-hydroxylase, converts 25OHD to 24,25-dihydroxyvitamin D [24,25$(OH)_2$ vitamin D], which promotes antiresorptive effects on bone and positive calcium balance. This sequence occurs less intensely with normal PTH, PO_4 (phosphate), and calcium levels. Calcitriol feeds back negatively on its own synthesis by suppressing 1-alpha-hydroxylase activity, stimulating 24-hydroxylase activity, decreasing PTH, and increasing calcium and phosphate. Calcitriol is also degraded primarily through the enzyme 24-hydroxylase. Renal 1-alpha-hydroxylase is most active, but this enzyme is also present in bone, brain, pancreas, heart, intestines, lymph nodes, adrenal gland, prostate, and other tissues (Fig. 18.2). Fibroblast growth factor 23 (FGF23) also has an important role in calcium and vitamin D metabolism.

7. What is the role of FGF23 in calcium, phosphate, and vitamin D metabolism?

FGF23 is a phosphaturic hormone produced by osteocytes in response to increases in serum levels of phosphate, 1,25$(OH)_2$ vitamin D, and PTH. By reducing proximal renal tubular phosphate reabsorption, stimulating 24-hydroxylase, inhibiting 1-alpha-hydroxylase, and inhibiting PTH synthesis and secretion by the parathyroid glands, FGF23 decreases serum phosphate, 1,25$(OH)_2$ vitamin D, and PTH. FGF23 levels rise significantly in chronic kidney disease (CKD) and are associated with higher mortality rates in CKD patients.

8. What is the function of the vitamin D receptor, and what are the classic and nonclassic effects of vitamin D?

Calcitriol is a hormone that classically helps regulate calcium and phosphate metabolism in the body. It acts on various organs such as the intestine, bone, kidneys, and parathyroid glands. Calcitriol activates the parathyroid glands' vitamin D receptor (VDR), reducing the production

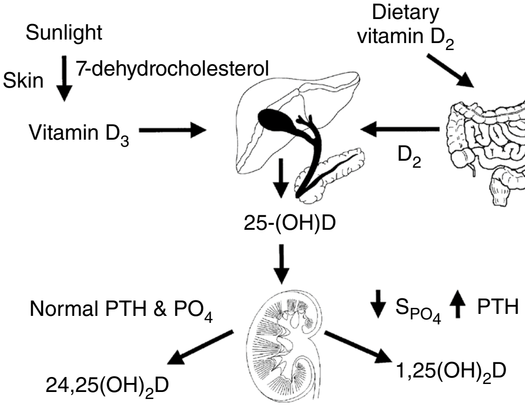

Fig. 18.2 Vitamin D metabolism. *PO4*, Phosphate; *PTH*, parathyroid hormone.

of PTH messenger RNA (mRNA) by inhibiting the pre-pro-PTH gene at the vitamin D response element. This inhibition decreases PTH synthesis within the chief cell of the parathyroid gland and ultimately lowers PTH levels. Calcitriol increases the absorption of calcium and phosphate in the intestine, resorption of calcium and phosphate in bones, turnover of bone tissue, and renal reabsorption of calcium and phosphate. The VDR is a nuclear hormone receptor regulated by calcium and PTH. Upon activation, the VDR regulates the expression of many proteins. Downregulated proteins include PTH, 1-alpha-hydroxylase, bone matrix protein, bone sialoprotein, type I collagen, interferons, interleukins, tumor necrosis factor (TNF), epidermal growth factor receptors, renin, and peroxisome proliferator-activated receptor (PPAR) gamma-2. Upregulated proteins include osteopontin, matrix Gla protein, type IV collagen, interleukins, VDR, calcium-sensing receptor (CaSR), and 24-hydroxylase. When the VDR is activated, calcitriol exhibits various nonclassic effects that are not necessarily related to calcium and phosphorus metabolism. These effects include the improvement of arterial calcification, the slowing down of neuronal degeneration, enhanced host defenses against bacterial infection and tumor growth, better Sertoli cell function and spermatogenesis, enhanced insulin synthesis and secretion from pancreatic beta cells, and assistance with glycogen and transferrin synthesis in liver parenchymal cells. Furthermore, calcitriol has antiproliferative and prodifferentiating effects on myeloid cell precursors, cardiac and smooth muscle cells, and various skin cell types, including keratinocytes, fibroblasts, hair follicles, and melanocytes.

9. What is the CaSR, and how does it affect calcium metabolism?

The CaSR is a membrane-bound calcium sensor–receptor. The most important locations of the CaSRs are the parathyroid glands and the renal tubular cells. CaSRs also occur in other tissues, including at low levels in pancreatic beta cells and thyroid C cells. The major function of the CaSR is to maintain extracellular calcium concentrations in the normal range and prevent hypercalcemia. In the parathyroid chief cells, the CaSR has a large extracellular domain of 700 amino acids (primary calcium binding site), a seven-segment transmembrane component, and a carboxyl-terminal cytoplasmic element of about 200 amino acids (primary effector site for metabolic changes). The CaSR belongs to subfamily C of the G protein-coupled receptor family. The CaSR senses the minutest change in ionized calcium (0.1 mg/dL) and regulates PTH secretion to maintain steady-state calcium levels within a narrow optimal range. These changes center on a set point for calcium-regulated PTH release unique to each individual. After activation by calcium, the CaSR activates phospholipase C, inhibits adenylate cyclase, and opens nonselective cation channels. This effect increases cytoplasmic calcium by mobilizing calcium from thapsigargin-sensitive intracellular stores and enhancing calcium influx through voltage-sensitive cation channels. These CaSR-induced changes in intracellular calcium act on the calcium response element of the pre-pro-PTH gene to decrease chief cell PTH mRNA synthesis, reduce PTH secretion, and decrease parathyroid gland hyperplasia. CaSR activation also activates the PAL cascade of phospholipase A2, arachidonic acid, and leukotrienes, degrading PTH stored in secretory granules.

The parathyroid glands secrete intact PTH (iPTH) and carboxy-terminal PTH (CPTH) fragments. Intact PTH acts directly on bone PTH receptors, releasing calcium from bone. CPTH remains in circulation much longer and at higher concentrations than iPTH. Although previously considered inactive, data now suggest that CPTH fragments can directly affect bone cells through a novel class of CPTH receptors. CPTH fragments accumulate in renal failure. PTH functions to keep calcium in the normal range and helps prevent hypocalcemia. Cinacalcet and etelcalcetide are calcimimetic drugs that bind, respectively, to the transmembrane and extracellular domains of the CaSRs, making the receptors markedly more responsive to ambient calcium.

10. What is the function of the CaSR in the kidneys?

In the kidney, as in the parathyroid glands, the CaSR functions to prevent hypercalcemia. Activation of the CaSR located on the basolateral membrane in the thick ascending limb of Henle's loop decreases tubular calcium reabsorption and increases excretion. Activation of the renal CaSR generates an arachidonic acid metabolite that inhibits the luminal potassium channel and the sodium-potassium adenosine triphosphatase (ATPase) pump on the basolateral membrane. This diminishes the lumen-positive electrical gradient needed for passive calcium and magnesium reabsorption. Thus, there is less reabsorption and more excretion of calcium. Because PTH is decreased by the CaSR activated in the parathyroid gland, there is less PTH-mediated distal tubular reabsorption of calcium, net calcium loss, and lower plasma calcium.

11. What are the overall effects of PTH, vitamin D, and FGF23 on calcium metabolism?

Plasma calcium is maintained within a narrow concentration range because it plays a key role in diverse physiologic processes, including intracellular signal transduction, muscle contraction, blood clotting, and neuronal transmission. Indeed, calcium in each person is so tightly regulated that the average daily ionized calcium level does not deviate by >0.3 mg/dL. Regulation of plasma calcium depends on normal amounts of PTH and calcitriol. Both hormones are also necessary for normal bone health. PTH and calcitriol provide the primary control of serum calcium. Both PTH and calcitriol increase bone resorption by increasing osteoclast activity. At physiologic levels, PTH and calcitriol also increase bone formation. Because osteoclasts have no known receptors for either hormone, PTH and calcitriol stimulate osteoclast activity indirectly. Both hormones promote normal bone formation by direct action on the osteoblast line of cells. PTH enhances the activity of osteoblasts, which secrete such factors as interleukin-6 (IL-6) that stimulate osteoclastic bone resorption. PTH and calcitriol promote osteoclast differentiation from promonocytes to monocytes to macrophages to preosteoclasts and finally to osteoclasts, increasing osteoclast number and activity and decreasing collagen synthesis. Calcitriol also increases calcium transport from bone to blood. It maintains a favorable calcium–phosphate product necessary for normal bone mineralization. Both PTH and calcitriol stimulate osteoblast production of receptor activator of nuclear factor kappa B ligand (RANKL). RANKL binds to its membrane-bound receptor (RANK) on preosteoclasts and osteoclasts. This action stimulates osteoclast differentiation and attachment to bone via integrins and, ultimately, bone resorption. PTH and calcitriol also control osteoblast production and secretion of osteoprotegerin (OPG), also called osteoclastogenesis inhibitory factor (OCIF), which blocks the effects of excess RANKL and promotes normal bone metabolism. This process depends on the concentration of PTH and calcitriol. Higher PTH and calcitriol levels increase bone resorption abnormally and may cause hypercalcemia and loss of bone mass.

While bone resorption is the major mechanism of most occurrences of hypercalcemia, PTH and calcitriol also act on the kidney to increase calcium reabsorption. PTH increases renal phosphate excretion, and calcitriol increases its reabsorption. PTH does not directly affect the intestine but increases calcitriol, which increases intestinal absorption of calcium and phosphate. Higher calcium and calcitriol levels provide negative feedback on PTH secretion, whereas higher phosphate levels provide positive feedback. The net effect is normal bone function and plasma calcium at physiologic levels of PTH and calcitriol, and loss of bone mineral and hypercalcemia at high levels. FGF23, a key player in this regulatory system, counters the effects of excess PTH and calcitriol by inhibiting the synthesis of both hormones and increasing renal phosphate excretion.

12. How do calcium and phosphate interact with calcium-regulating hormones?

Table 18.2 summarizes the key factors controlling serum calcium. The arrows show direct actions of factors in the left column on factors in the top row, whereas the plus (+) and minus (−) signs show indirect actions. Usually, the direct effects predominate as the net effect. Table 18.3 outlines the specific effects of each of these factors.

TABLE 18.1 Mechanisms and Causes of Hypercalcemia

PRIMARY MECHANISM	CAUSE(S) OF HYPERCALCEMIA
Increased bone resorption	Hyperparathyroidism Local osteolytic hypercalcemia Humoral hypercalcemia of malignancy Thyrotoxicosis Pheochromocytoma Excessive vitamin A (usually >25,000 IU/day) Lithium carbonate Immobilization Addison's disease
Increased renal reabsorption or decreased excretion	Milk-alkali syndrome Rhabdomyolysis Thiazide diuretics Familial hypocalciuric hypercalcemia Renal failure Lithium carbonate Addison's disease (volume contraction)
Increased gut absorption	Excessive vitamin D (usually >10,000 IU/day) Berylliosis Candidiasis, coccidioidomycosis Eosinophilic granuloma Histoplasmosis Sarcoidosis Silicone implants Tuberculosis Inflammatory disorders Acquired immunodeficiency syndrome Lymphomas

13. What are the major causes of hypercalcemia?

Hyperparathyroidism and malignancy cause 90% of hypercalcemia. These and other causes include the following.

Causes of Hypercalcemia

- Primary hyperparathyroidism
- Malignancy
- Tertiary hyperparathyroidism
- Familial hypocalciuric hypercalcaemia
- Thyrotoxicosis
- Adrenal insufficiency
- Pheochromocytoma
- Paget's disease
- Hypervitaminosis D
- Hypervitaminosis A
- Sarcoidosis
- Nonmalignant granulomatous disease
- Acquired immunodeficiency syndrome
- Systemic Inflammatory Response Syndrome (SIRS)
- Rhabdomyolysis
- Thiazide diuretics
- Lithium
- Theophylline toxicity
- Milk-alkali syndrome
- Immobilization

TABLE 18.2 Interaction of Factors Controlling Serum Calcium

	PTH	$1,25(OH)_2D$	CALCITONIN	CALCIUM	PO_4
Parathyroid hormone (PTH)	—	↑+	+	↑+	↓↑+
$1,25(OH)_2D$	↓−	↓−	+	↑	↑
Calcitonin	+	+	—	↓	↓
Calcium	↓	↓	↑	—	↓
Phosphate (PO_4)	↑+	↓	—	↓	—
Fibroblast growth factor-23 (FGF-23)	↓+	↓+	—	− +	↓−

Arrows (↑, increase; ↓, decrease) indicate direct effects; + and – indicate indirect effects; — indicates no effect.

TABLE 18.3 Summary of Calcium and Phosphate Control

VARIABLE	DIRECT ACTION(S)
Parathyroid hormone (PTH)	Increased bone resorption of calcium and phosphate Increased distal renal tubular calcium reabsorption Decreased renal tubular phosphate reabsorption Increased renal production of $1,25(OH)_2$ vitamin D Net effect: increased serum calcium and decreased phosphate
$1,25(OH)_2$ vitamin D	Increased bone resorption of calcium and phosphate Increased renal reabsorption of calcium and phosphate Increased gut absorption of calcium and phosphate Decreased parathyroid production of PTH Decreased renal production of $1,25(OH)_2$ vitamin D Net effect: increased serum calcium and phosphate
Calcitonin	Decreased bone resorption of calcium and phosphate Decreased renal reabsorption of calcium and phosphate Decreased gut absorption of calcium and phosphate Net effect: decreased serum calcium and phosphate
Calcium	Decreased PTH synthesis and secretion Decreased $1,25(OH)_2$ vitamin D production in the kidney Increased calcitonin release from the thyroid C cells Decreased phosphate
Phosphate	Decreased $1,25(OH)_2$ vitamin D production in the kidney Decreased calcium Increased PTH synthesis in parathyroid chief cells
Fibroblast growth factor 23 (FGF23)	Decreased $1,25(OH)_2$ vitamin D production in the kidney Decreased renal tubular phosphate reabsorption Decreased parathyroid production of PTH

14. How do various causes of hypercalcemia increase the serum calcium level?

True hypercalcemia results from altered bone resorption, renal tubular reabsorption, and gut absorption of calcium. Although the bone (resorption and formation), kidney (reabsorption and excretion), and gut (absorption and secretion) each have two major processes involved with mineral metabolism, only resorption, reabsorption, and absorption play a significant role in hypercalcemia. An exception to this rule occurs when decreased renal function from renal or prerenal disease impairs calcium filtration and excretion. In Fig. 18.3, solid arrows represent potential causes of increased calcium, and dashed arrows represent potential causes of decreased calcium.

15. What are the mechanisms and causes of hypercalcemia?

From the preceding discussions, one can appreciate that mechanisms of hypercalcemia are usually multifactorial. However, most hypercalcemic syndromes have a primary or predominant mechanism,

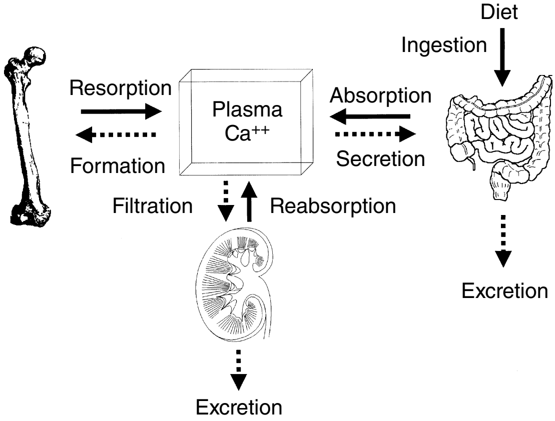

Fig. 18.3 Calcium (Ca^{++}) metabolism. Solid arrows represent potential causes of increased calcium, and dashed arrows represent potential causes of decreased calcium.

as outlined in Table 18.1. Most resorptive hypercalcemia is humoral (PTH, PTH-related peptide [PTHrP], transforming growth factor-alpha [TGF-alpha], TNF) or local osteolytic hypercalcemia (PTHrP, interleukins, prostaglandins). Increased calcium absorption usually occurs because of high 1,25$(OH)_2$ vitamin D levels produced by tumors or granulomas and from hypervitaminosis D from excess 25OHD and its conversion to 5,6-trans 25OHD that result from excessive vitamin D_3 or vitamin D_2 intake. Ninety percent of hypercalcemia cases result from hyperparathyroidism or cancer.

16. What is the relative frequency of skeletal lesions in patients with advanced cancer?

The relative frequency in advanced cancer is myeloma (95–100%), breast and prostate (70%), thyroid (60%), bladder (40%), lung (35%), renal (25%), and melanoma (14–45%). Common sites of bone metastases are ribs, spine, pelvis, and proximal extremities.

17. What is the incidence of hypercalcemia in patients with cancer?

Hypercalcemia affects 15% to 30% of patients with cancer. It is most common in squamous cell carcinoma of the lung, head and neck, renal cell carcinoma, breast cancer, multiple myeloma, and lymphoma. About 80% of cancer-related hypercalcemia results from humoral causes and 20% from metastases to bone.

18. What multiple endocrine neoplasia syndromes (MEN) are associated with hypercalcemia?

The four familial multiple endocrine neoplasia (MEN) syndromes associated with hyperparathyroidism and hypercalcemia are MEN1, MEN2A, MEN 2B, and MEN4. These syndromes are described in detail in Chapter 19, Question 10. In comparison with sporadic hyperparathyroidism, parathyroid tumors in MEN syndromes are more often bilateral and hyperplastic.

19. How would you diagnose familial hypocalciuric hypercalcemia?

Familial hypocalciuric hypercalcemia (FHH), also known as familial benign hypercalcemia, results from autosomal dominant mutations in the CaSR gene. These mutations produce defective CaSRs on parathyroid and renal tubular cell membranes that are less responsive to ambient calcium. Key diagnostic features of FHH include asymptomatic presentation, a positive family history of benign hypercalcemia, mild hypercalcemia, normal-to-high serum PTH levels, and decreased urinary calcium with low urine calcium to creatinine clearance ratio (UCCR) that is usually <0.01 or fractional excretion of calcium (FECa) (<1%). Distinguishing FHH from primary hyperparathyroidism (PHPT) is crucial to avoid unnecessary and ineffective parathyroidectomy. Patients with PHPT usually exhibit a UCCR >0.02 or FECa >2%. Patients with FHH typically have a 24-hour urinary calcium level <50 mg/24 hr compared to >200 mg/24 hr for those with PHPT. Urinary calcium excretion in up to 20% of patients with FHH may be normal.

So, family history is important, and genetic testing for CaSR gene mutations may be required for diagnosis.

20. What is the likely cause of hypercalcemia in the following patient?

An 18-year-old man has had serum calcium values of 10.5 to 11.8 mg/dL for 2 years. His history and physical examination are normal, and he has a family history of hypercalcemia. Current laboratory values are calcium 11.5 mg/dL, intact PTH 70 pg/mL (normal NL <65), plasma creatinine (PCr) 1.0 mg/dL, random urine calcium (UCa) 5 mg/dL, and urine creatinine (UCr) 90 mg/dL.

$$\text{Ca/Cr clearance ratio} = [\text{UCa} \div \text{PCa}] \times [\text{PCr} \div \text{UCr}]$$
$$\text{Ca/Cr Clearance ratio} = [5 \text{ mg/dL} \div 11.5 \text{ mg/dL}] \times [1 \text{ mg/dL} \div 90 \text{ mg/dL}] = 0.005$$
$$\text{FECa} = 0.005 \times 100\% = 0.5\%$$

The history, family history, physical findings, laboratory values, and UCCR <0.01 with FECa <1% support the diagnosis of FHH.

21. What therapy is useful for severe hypercalcemia?

Most patients with severe hypercalcemia require treatment with multiple drugs. The goal is to use the lowest dose and frequency possible to achieve and maintain acceptable serum calcium levels. The usual therapy order is normal saline, calcitonin, zoledronic acid, and glucocorticoids if needed. Furosemide is used to improve urinary volume and should be given only to treat and avoid volume overload. Bisphosphonates are relatively contraindicated with GFR <30 mL/min per 1.73 m^2. Denosumab is a monoclonal antibody to RANKL that is FDA-approved to treat hypercalcemia of malignancy refractory to bisphosphonate therapy. Denosumab is not cleared by the kidney and may be used when zoledronic acid is ineffective or contraindicated, as in renal failure. However, one should exercise caution when the glomerular filtration rate (GFR) is <30 mL/min per 1.73 m^2 and closely monitor patients for hypocalcemia for several weeks after administration. Consult with nephrology for dialysis treatment for patients with renal failure and those with severe and refractory hypercalcemia and hypercalcemic crisis. See Table 18.4.

22. Describe the mechanisms of action of drug therapies for hypercalcemia.

See Table 18.5.

23. How might calcimimetic drugs be useful in therapy for hypercalcemia?

Two FDA-approved calcimimetics bind to the extracellular domains of CaSRs on parathyroid cells and enhance chief cell responsiveness to extracellular calcium. This effect shifts the PTH–calcium curve to the left, increasing parathyroid cell sensitivity to the PTH-suppressive effects of high extracellular calcium and decreasing responsiveness to the PTH-stimulatory effects of low calcium (see Questions 8 and 9). Cinacalcet is an oral calcimimetic that binds to the transmembrane domain of the CaSR and is FDA-approved to treat secondary HPT in patients with end-stage renal disease on dialysis, parathyroid carcinoma, and hypercalcemia in patients with primary HPT who cannot undergo parathyroidectomy.

Etelcalcetide is an intravenous calcimimetic that binds to the extracellular domain of the CaSR at a site different from that of calcium; it is FDA-approved to treat secondary HPT in adults with CKD on hemodialysis. Both calcimimetics decrease serum levels of PTH and calcium. Etelcalcetide is more effective. By increasing CaSR calcium sensitivity in Henle's loop, cinacalcet also increases renal calcium excretion. Although not approved for the following uses, cinacalcet has improved persistent HPT after kidney transplantation, hypercalcemia caused by FHH, and lithium-induced hypercalcemia (see Question 24). The net effect of calcimimetics is a dose-dependent reduction in PTH secretion, an increase in urinary calcium excretion, and a decrease in serum calcium. Use cinacalcet with caution in patients with hypercalciuria and monitor urinary calcium.

24. How does lithium cause hypercalcemia?

Lithium decreases urinary calcium through competitive inhibition of the CaSR in the thick ascending limb of Henle's loop, causing increased calcium reabsorption, decreased calcium

TABLE 18.4 Therapy for Hypercalcemia

THERAPY	DOSE	ROUTE	MONITOR/COMMENT
Saline	250–1000 mL/hr	IV	Cardiopulmonary function with examination, central venous pressure and chest radiograph, daily weights, and input/output.
Furosemide	20–80 mg every 2–4 hr or 40 mg/hr CI	IV	Serum and urine electrolytes. Replace K, Mg, and PO_4 based on serum levels and urinary losses. Only to prevent volume overload.
Salmon calcitonin	4–8 IU/kg every 6–12 hours	IM, SC	Allergic reaction. Give a skin test of 1 IU intradermally before treatment. Effective only during first 48–72 hr.
Prednisone/ methylprednisolone	40–60 mg daily for 10 days	PO/IV	Possible adjunct to calcitonin. Effective in $1,25(OH)_2$ vitamin D-associated hypercalcemia.
Zoledronic acid	4 mg IV over 20–30 minutes, may repeat in 7 days then every 2–4 weeks PRN	IV	Drug of choice for malignancy-associated hypercalcemia. Dosage is decreased in stage 3 CKD to 3–3.5 mg. Avoid use for GFR <30 mL/min. Monitor GFR. Hold for >0.5 mg/dL increase in creatinine.
Pamidronate	60–90 mg over 2–24 hours every 1–3 weeks PRN	IV	Infuse 60 mg over 6–8 hours for GFR <30 mL/min as one-time dose only and monitor GFR. Hold for >0.5 mg/dL increase in creatinine.
Cinacalcet	30–90 mg 2–4 times daily	PO	Take with meals. Titrate every 2–4 weeks based on calcium and PTH measured at least 12 hr after dose.
Denosumab	120 mg every 4 weeks and days 8 and 15 of the first month of therapy	SC	For treatment of hypercalcemia of malignancy refractory to bisphosphonates. Takes 4–7 days for effect. Consider decreased dosage and frequently monitor for hypocalcemia when patient has vitamin D deficiency and GFR <30 mL/min.
Dialysis	Low or no calcium dialysate	Hemodialysis Peritoneal dialysis	Hypercalcemic crisis or refractory hypercalcemia. Useful in renal failure. Nephrology consultation.

b.i.d., Twice daily; *CI*, continuous infusion; *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate; *IM*, intramuscularly; *IV*, intravenously; *K*, potassium; *Mg*, magnesium; *Na*, sodium; *PO*, orally; *PO4*, phosphate; *PRN*, as needed; *q.i.d.*, four times daily; *SC*, subcutaneously.

excretion, and hypercalcemia. Urinary calcium may be low in lithium-treated patients, as it is in patients with FHH. Lithium also reduces the sensitivity of the parathyroid CaSR to calcium and shifts the PTH–calcium curve in the parathyroids to the right. Thus, for any given calcium level, there is less calcium suppression of PTH secretion and synthesis and higher serum PTH levels. Compared to PHPT, lithium-treated patients typically have normal phosphorus and higher magnesium levels. Because hypercalcemia and elevated PTH may persist after lithium is discontinued, therapy other than just discontinuing lithium may be indicated if the hypercalcemia is symptomatic. Cinacalcet has successfully corrected or ameliorated PTH and serum calcium levels in such patients. This effect is expected because cinacalcet sensitizes the CaSR to calcium and shifts the PTH-calcium curve to the left.

TABLE 18.5 Mechanisms of Action of Hypercalcemic Therapy

DRUG	MECHANISM(S) OF ACTION
Saline	Dilutes serum calcium by volume expansion and increases urinary flow and calcium excretion.
Furosemide	Impairs renal sodium and calcium reabsorption in Henle's loop, increasing urinary flow and calcium excretion.
Calcitonin	Binds to receptors on osteoclasts, inhibiting osteoclast activity and decreasing bone resorption; also decreases renal reabsorption.
Glucocorticoids	Antagonism of vitamin D, causing decreased calcium absorption and reabsorption; in tumoral states, may be tumor lytic and may decrease production of osteoclast-activating factors and vitamin D.
Bisphosphonates	Impair osteoclast differentiation, recruitment, motility, and attachment; incorporate into bone matrix, making the matrix resistant to hydrolysis; overall effect is decreased bone resorption.
Cinacalcet	Calcimimetic that binds to the calcium-sensing receptor, making it markedly more responsive to calcium activation decreasing parathyroid hormone (PTH) and calcium.
Denosumab	Monoclonal antibody that binds to receptor activator of nuclear factor kappa B ligand (RANKL), preventing activation of the osteoclast RANK receptor and decreasing osteoclast bone resorption.
Dialysis	Direct removal of calcium from blood.

Note: For long-term hypocalcemic effects, drug therapy for hypercalcemia must antagonize one of the three main causes of hypercalcemia: bone resorption, renal reabsorption, or gut absorption. All hypercalcemia results from some abnormality in one of the three. Thus, one of these etiologies should be considered in the choice of drug therapy. As noted, most drug therapies for hypercalcemia impair bone resorption.

KEY POINTS

Hypercalcemia

- Therapy for hypercalcemia should target the underlying etiology, including excess bone resorption, renal tubular reabsorption, and gut absorption.
- Although there are >30 different causes of hypercalcemia, hyperparathyroidism and hypercalcemia of malignancy account for >90% of cases.
- Most patients with severe hypercalcemia require normal saline hydration and multiple-drug therapy. However, most therapies for hypercalcemia inhibit bone resorption.
- Zoledronic acid is the most potent bisphosphonate approved for treating hypercalcemia. It has the advantage over pamidronate because of shorter infusion time and a longer duration of action.
- Cinacalcet is a calcimimetic that lowers serum parathyroid hormone (PTH), calcium, and phosphorus levels. It is approved for treating secondary hyperparathyroidism (HPT), parathyroid carcinoma, and primary HPT in patients with significant hypercalcemia when parathyroidectomy is not clinically appropriate. Although not approved for such situations, cinacalcet also lowers PTH and calcium in kidney transplant recipients who have persistently elevated PTH.

WEBSITES

Hypercalcemia of Malignancy:
https://www.aub.edu.lb/fm/CaMOP/publications/A-Systematic-Review-Supporting-Endocrine-Society-Clinical-Practice-Guideline-Treatment-Hypercalcemia-Malignancy-Adults.pdf
Denosumab: a new agent in the management of hypercalcemia of malignancy: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4976858/
Familial hypocalciuric hypercalcemia: https://rarediseases.info.nih.gov/diseases/10828/familial-hypocalciuric-hypercalcemia

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CHAPTER 19

Hyperparathyroidism

Leonard R. Sanders

1. What is hyperparathyroidism?

Hyperparathyroidism (HPT) is a clinical disorder of calcium metabolism associated with increased bone resorption and specific symptoms and signs that result from excessive parathyroid hormone (PTH), hypercalcemia, or altered vitamin D, phosphate, and fibroblast growth factor 23 (FGF23) metabolism. There are three types of HPT: primary, secondary, and tertiary.

2. How common is primary HPT (PHPT)?

Primary HPT (PHPT) is the principal cause of HPT. PHPT affects about 0.85% of the general population, 1.2% of women, up to 2% of postmenopausal women, and 0.5% of men. Increasing calcium intake may reduce this occurrence.

3. What causes PHPT?

PHPT occurs when the normal suppression of PTH by calcium decreases, leading to excessive PTH secretion and hypercalcemia. The cause of most PHPT is a benign tumor in one or more parathyroid glands. The exact etiology of most PHPT is unknown. However, it is associated with radiation exposure, prolonged use of lithium, genetic mutations affecting MEN1, CDC73, and CaSR genes, and genomic rearrangements that involve structural alteration of chromosomes. Parathyroid adenomas and hyperplasia may exhibit reduced expression of the CaSR, an increase in the calcium set point, a decrease in PTH suppression, and an increase in PTH associated with a rightward shift in the calcium-PTH curve.

4. What anatomic alterations occur in PHPT?

Most patients with PHPT typically have a single parathyroid adenoma, accounting for 80–85% of cases. Four-gland hyperplasia occurs in 10–15% of patients, while multiple adenomas occur in 2–4% of cases. Parathyroid carcinomas are rare, accounting for less than 0.5% of cases.

Over 95% of patients with parathyroid adenomas have only one adenoma, while less than 5% have two or more. The average normal parathyroid gland is 0.5 × 0.3 × 0.1 cm and weighs 30 to 40 mg. The average weight of parathyroid adenomas is 500 mg, but this can vary depending on the life span of the adenoma. Some adenomas can weigh as much as 5 to 25 g. The largest reported tumor weighed 120 g, and the highest number of glands found in one patient was eight. Parathyroid adenomas are usually present in the same location as normal glands. However, they can also occur elsewhere, including within the thyroid gland, superior mediastinum, thymus, esophagus, retroesophageal space, pharynx, and lateral neck.

5. How do you diagnose PHPT?

Persistent hypercalcemia, elevated or high-normal serum PTH levels, and normal-to-high urinary calcium suggest PHPT. When a patient has hypercalcemia, suspect PHPT as it is the most common cause. Specific symptoms or signs are usually absent. PHPT can present in three ways: classic PHPT with elevated calcium and PTH in 80–90% of patients, nonclassic PHPT with elevated calcium and normal PTH in 10–20% of patients, and normocalcemic PHPT with normal calcium and elevated PTH in 1–4% of patients.

6. How does age complicate the diagnosis of HPT?

The laboratory reference ranges for intact PTH (10–65 pg/mL) and calcium (8.5–10.5 mg/dL) can vary between older adults and young individuals. These ranges can also differ among different laboratories. The PTH and calcium reference ranges are not age-adjusted for adults. However, for adults under 45 years, an intact PTH reference range of 10–45 pg/mL may be more appropriate. As people age, PTH levels increase and calcium levels decrease. The reasons for this may be declines in renal function, vitamin D synthesis, and the absorption of vitamin D and calcium. When calcium is high and PTH levels are within the normal upper range, it is more likely to indicate primary hyperparathyroidism (PHPT) in patients younger than 50 than those older. The decline in serum calcium levels with age is usually because of the decrease in albumin and does not affect serum PTH levels.

7. How might you confirm the diagnosis of PHPT before recommending parathyroidectomy?

Obtain at least three fasting serum calcium levels and two PTH measurements several weeks apart. It is important to account for the patient's renal function and to stop any thiazide diuretics for at least 1 week before the measurements. If safe, also discontinue lithium. Measure serum total calcium and correct the calcium for changes in albumin and total protein levels (see Chapter 18). If there are any concerns about true hypercalcemia, measure an ionized calcium. If repeated serum calcium levels are elevated and the PTH is high or high-normal, PHPT is usually present. If a patient has normal calcium levels but high PTH, it may indicate normocalcemic PHPT (NPHPT). However, before confirming NPHPT, it is necessary to thoroughly investigate for secondary HPT caused by factors such as renal insufficiency, vitamin D deficiency, inadequate calcium intake, renal calcium leak, and others. Make sure to exclude vitamin D deficiency by ensuring that 25-hydroxy (OH) vitamin D levels are above 30 ng/mL. Most labs use second-generation PTH assays, such as the immunoradiometric assay (IRMA) and the immunochemiluminometric assay (ICMA), which are reliable for diagnosis but may overestimate PTH concentrations in chronic kidney disease (CKD) and detect both the 1-84 intact PTH and the C-terminal or N truncated 7-84 fragment that accumulates in CKD. Third-generation PTH assays, such as the cyclase-activating PTH IRMA and bio-iPTH chemiluminescent (CLIA) assays, specifically target the amino-terminal 1 to 6 amino acids of the PTH 1-84. These assays are designated whole, bioactive, intact PTH assays and are more specific for the intact 1-84 PTH. However, these more expensive assays have not shown a clinical benefit over the second-generation assays.

8. What lab studies or conditions help with the differential diagnosis of PHPT?

Increased serum chloride (Cl) and decreased or low-normal phosphate (PO_4) levels, increased Cl/PO_4 ratio >33, elevated urinary pH (6.0), and increased serum alkaline phosphatase can support the diagnosis of primary hyperparathyroidism (PHPT), but these findings are not specific. If the measured parathyroid hormone (PTH) levels are lower than expected, ensure the patient is not taking excess biotin (vitamin B7) that can falsely lower PTH levels by interfering with standard PTH assays. To confirm the diagnosis, repeat the PTH measurement after the patient has been off biotin for 3–5 days. If the PTH levels are still lower than expected for PHPT in patients with hypercalcemia (<20 pg/mL), it is essential to consider other causes of hypercalcemia, including cancer (see Chapter 18).

9. What differentiates familial hypocalciuric hypercalcemia (FHH) from PHPT?

Familial hypocalciuric hypercalcemia (FHH) is a condition resulting from genetic mutations. It is also known as autosomal dominant familial benign hypercalcemia and is classified into three types. FHH1 is caused by a mutation in the *CaSR* gene that encodes the CaSR protein, FHH2 by a mutation of the *GNA11* gene that encodes the G protein subunit Ga11, and FHH3 by a mutation of the *AP2S1* gene that encodes the sigma subunit of the adaptor-related protein complex 2. The latter is necessary to move the *CaSR* from the cytosol into the plasma membrane for calcium activation. If there is a family history of hypercalcemia, particularly at a young age, and chronically elevated levels of serum calcium and PTH, it is necessary to consider FHH. There is a 50% likelihood that a first-degree relative has FHH. To confirm FHH, calculate the fractional excretion of calcium (FECa). In patients with FHH, urinary calcium is usually less than 50–100 mg/24 hr, urine calcium/creatinine ratio is less than 0.01, and FECa is less than 1%. In contrast, patients with PHPT have urinary calcium greater than 100–200 mg/24 hr, urine calcium/creatinine ratios greater than 0.02, and FECa greater than 2%. When young patients present with hypercalcemia, elevated PTH, hypocalciuria, or a family history of hypercalcemia, it is important to suspect FHH and test the family. Positive tests in the patient and family strongly suggest FHH. However, low urinary calcium occurs in only 85% of patients with FHH, and clinical lab tests in FHH can overlap those with PHPT. Genetic testing for inactivating mutations of the *CaSR*, *GNA11*, and *AP2S1* genes may be required to confirm the diagnosis. Neck exploration is not recommended in FHH, as it does not correct hypercalcemia.

10. What familial or genetic syndromes are associated with PHPT?

Several genetic or familial syndromes may be linked to PHPT. When younger patients present with PHPT, it is essential to consider genetic-associated PHPT and genetic testing for diagnosis. One such syndrome is MEN 1, also known as Wermer's syndrome, which has autosomal dominant (AD) inheritance and is associated with a loss-of-function mutation in the MEN 1 menin tumor suppressor gene. MEN 1 affects tumors of the "3Ps," including parathyroid, pituitary, and pancreas, resulting in parathyroid hyperplasia and often prolactinomas and gastrinomas. AD MEN 4 is clinically indistinguishable from MEN 1. However, MEN 4 results from an inactivating mutation of the CDKN1B gene, presents much later in adulthood, and is less common and less progressive.

An abnormality of the RET proto-oncogene causes Sipple's syndrome, or AD MEN 2A, which is associated with medullary thyroid carcinoma (MCT), pheochromocytoma, and hyperparathyroidism. AD MEN 2B involves MCT, pheochromocytoma, and multiple neuromas but no hyperparathyroidism. The AD hyperparathyroidism-jaw-tumor syndrome (HPT-JT) is associated with a defect in the HRPT2/CDC73 gene characterized by parathyroid adenomas, 15–20% of the time parathyroid carcinomas, ossifying fibromas of the jaw, renal abnormalities, and uterine tumors. Finally, familial isolated hyperparathyroidism (FIHP) is usually associated with PHPT from a parathyroid adenoma caused by mutations in the MEN 1 gene, CDC73, HPRT2, and CaSR. Incomplete penetrance of FIHP occurs in 20–80% of cases, depending on the specific gene mutations.

11. How does CKD complicate the diagnosis of PHPT?

When the glomerular filtration rate (GFR) is below 30–40 mL/min, CKD can cause laboratory abnormalities and symptoms similar to PHPT. CKD leads to relative hypocalcemia due to increased serum phosphate and decreased calcitriol (see question 18). These changes directly stimulate the parathyroid gland to produce more PTH, resulting in secondary hyperparathyroidism (SHPT). The PTH 7-84 C-terminal PTH fragment accumulates in CKD and interferes with commonly used intact PTH assays. As a result, patients with CKD have higher levels of measured intact PTH compared to normal subjects. Diagnosing PHPT in patients with renal failure can be challenging because both SHPT from CKD and PHPT have elevated PTH and overlapping levels of calcium and can have similar symptoms of lethargy, depression, anorexia, nausea, constipation, and weakness. However, a critical difference between the PHPT and SHPT of CKD is high to high-normal serum phosphate levels in CKD. So, always measure phosphate levels in patients with CKD and suspected PHPT.

12. What are the symptoms and signs of PHPT?

Most patients (85%) with PHPT do not show any symptoms, but some may experience vascular, musculoskeletal, gastrointestinal, and neurologic symptoms. These symptoms are often described as "kidney stones, painful bones, abdominal groans, psychic moans, and fatigue overtones." Nephrolithiasis, or kidney stones, occurs in approximately 10% to 20% of PHPT cases. PHPT is present in 5% of people with calcium stones. Proximal muscle weakness is also a common characteristic. Table 19.1 contains more characteristic symptoms and signs.

13. What is band keratopathy?

Band keratopathy is a classic but unusual sign of PHPT characterized by an irregular region of calcium phosphate deposition at the medial and lateral limbic margins of the outer edges of the corneas. The location is caused by diffusion of carbon dioxide from the air-exposed areas of the cornea, leaving an alkaline environment that favors precipitation of calcium phosphate crystals. Band keratopathy occurs with a high-calcium-phosphate product. Diagnosis is made by ophthalmologic slit lamp examination. The sign differs from arcus senilis, an age-related, linear, concentric gray crescent separated from the extreme periphery (limbus corneae) by a rim of the clear cornea that, with time, completely encircles the cornea.

TABLE 19.1 Hyperparathyroidism: Symptoms and Signs and Their Probable Causes

SYMPTOMS AND SIGNS	PROBABLE CAUSE(S)
Renal: hypercalciuria, nephrolithiasis, nephrocalcinosis, polyuria, polydipsia, renal insufficiency, and distal renal tubular acidosis (RTA)	Parathyroid hormone (PTH) stimulates bone resorption, hypercalcemia, bicarbonaturia, and phosphaturia, causing decreased tubular responsiveness to antidiuretic hormone (ADH), polyuria, calcium oxalate and phosphate crystallization, nephrocalcinosis, RTA, and renal insufficiency.
Neuromuscular: weakness, myalgia	Prolonged excessive PTH and associated metabolic changes may cause direct neuropathy and myopathy with abnormal nerve conduction velocities (NCVs) and characteristic electromyographic changes and myopathic features on muscle biopsy.
Neurologic and psychiatric: memory loss, depression, psychoses, neuroses, confusion, lethargy, fatigue, paresthesias	PTH and calcium excess cause peripheral neuropathy with abnormal NCVs and central nervous system damage with abnormal electroencephalographic changes.
Skeletal: bone pain, osteitis fibrosa, osteoporosis, and subperiosteal skeletal resorption	PTH increases bone resorption and acidosis with subsequent bone buffering and bone loss of calcium and phosphate.
Gastrointestinal: abdominal pain, nausea, heartburn, peptic ulcer, constipation, and pancreatitis	Hypercalcemia stimulates gastrin secretion, decreases peristalsis, and increases the calcium–phosphate product with calcium–phosphate deposition in and obstruction of pancreatic ducts.
Hypertension	PTH and hypercalcemia are associated with increased vasoconstriction.
Arthralgia, synovitis, arthritis	HPT is associated with increased crystal deposition from calcium phosphate (paraarticular calcification), calcium pyrophosphate (pseudogout), and uric acid/urate (gout)
Band keratopathy	Calcium–phosphate precipitation occurs in the medial and limbic margins of the cornea.
Anemia	Unknown—but may be associated with bone marrow fibrosis and impaired erythropoiesis.

14. What are the classic radiographic findings in PHPT?

The classic radiographic findings in patients with PHPT are salt-and-pepper skull, subperiosteal bone resorption along the radial aspect of the middle and distal phalanges of the index and middle fingers and distal clavicles, tufting of the distal phalanges with pseudo-clubbing, osteitis fibrosa cystica with brown tumors, chondrocalcinosis from joint deposition of calcium pyrophosphate crystals, and loss of the lamina dura. Due to early diagnosis of PHPT, these radiographic findings are often not found. Prolonged PHPT can cause osteopenia and osteoporosis.

15. What is the differential diagnosis of PHPT?

PHPT presents with hypercalcemia, so the initial differential diagnosis is the same as for hypercalcemia (see Chapter 18). Symptoms and signs can help determine the cause of hypercalcemia. If hypercalcemia is mild and the findings are nonspecific, PHPT is likely. The two most common causes of hypercalcemia are PHPT and malignancy. About 15% to 30% of cancer patients develop hypercalcemia, usually with symptoms. In HHM, the tumor produces a PTH-like hormone called PTH-related peptide.

16. What laboratory tests help distinguish the three types of HPT?

See Table 19.2 and question 22.

17. What pathophysiologic changes occur in PHPT?

PHPT leads to excessive PTH secretion from parathyroid adenomas, hyperplasia, or, rarely, carcinoma. The increased PTH causes bone resorption by activating osteoclasts (question 11, Chapter 18), distal renal tubular calcium reabsorption, and calcitriol production by stimulating

TABLE 19.2 Parathyroid Hormone (PTH) and Calcium Levels in Hyperparathyroidism

TYPE OF HYPERPARATHYROIDISM	PTH	CALCIUM*
Primary	↑ Normal	↑ Normal
Secondary	↑	↓ Normal
Tertiary	↑↑	↑

↑, High; ↑↑, very high. *Calcium is usually high in PHPT, but calcium may be normal, and PTH is high in normocalcemic PHPT.

renal 1-alpha-hydroxylase, which increases intestinal calcium absorption. All three processes contribute to hypercalcemia.

PTH enhances calcium reabsorption in renal distal tubular cells (DTC) by increasing the activity of the transient receptor potential vanilloid 5 (TRPV5) calcium channel, stimulating basolateral calcium ATPases and the sodium-calcium exchanger, and inducing the expression of calbindin-D28k, a calcium-binding protein. These actions facilitate calcium entry into the DTC, its movement from the cells into the bloodstream, and creation of a positive luminal charge that drives paracellular calcium reabsorption. Both PTH and 1,25 (OH)2D regulate calcium reabsorption. The kidney filters calcium, with 60–70% passively reabsorbed in proximal tubular cells (PTC) and another 20–25% reabsorbed within Henle's loop. PTH and 1,25 (OH)2D regulate reabsorption in the remaining 8–10% of calcium in the DTC.

Calcium reabsorption in the late distal tubule relies on specific proteins, including TRPV5, an apical epithelial calcium channel, and calbindin-D28K, which binds to subapical Ca^{++} ions. These proteins enable calcium to enter the DTC and be transported across the cell.

The late distal tubule also contains basolateral plasma membrane calcium ATPase(s) (PMCAs) and the basolateral Na^{+}/Ca^{++} exchanger-1 (NCX1). Calcium reabsorption primarily occurs through TRPV5, with subapical Ca^{++} ions binding to intracellular calbindin-D28K for transport to the basolateral membrane. Calcium is then expelled from the cell against a steep electrochemical gradient, mainly by NCX1 (70% of Ca^{++} flux) and PMCA. PTH is the primary hormonal regulator of essential proteins for calcium reabsorption in the DTC, including TRPV5, calbindin-D28K, and PMCA. 1,25 (OH)2D also enhances the expression of these proteins, indicating that DTC calcium reabsorption is under dual hormonal regulation. PTH also stimulates the rapid endocytosis of the PTC type II sodium-phosphate cotransporter (Npt2a), causing its internalization and subsequent degradation by lysosomes within the PTC. As a result, there is a rapid decrease in phosphate reabsorption and phosphaturia.

18. What pathophysiologic changes occur in SHPT?

Secondary hyperparathyroidism (SHPT) occurs when the body compensates for low calcium, high phosphorus, low calcitriol, and excess FGF23 by secreting more PTH. The increased PTH helps normalize free calcium levels. The main cause of SHPT is renal failure, which leads to increased PTH secretion due to all four factors mentioned. In renal failure, the kidneys cannot properly excrete phosphorus, leading to increased levels. The increased phosphorous stimulates PTH secretion, lowers ionized calcium levels, decreases 1,25 (OH)2D, and increases FGF23 secretion. The decreased calcium and 1,25 (OH)2D further enhance the synthesis and secretion of PTH.

It is important to control phosphorus levels through diet, phosphate binders, and vitamin D supplementation to delay the onset of SHPT in renal failure. Stimulating the parathyroid cell CaSR, vitamin D receptor (VDR), and FGF23 receptor (FGFR) can reduce PTH secretion through negative feedback. Relative hypocalcemia (mid-low normal calcium) can also cause SHPT. Some causes of hypocalcemia include vitamin D deficiency, dietary calcium malabsorption (related to age or gastric bypass), inadequate calcium intake, and renal calcium leak. SHPT is associated with parathyroid hyperplasia, where the parathyroid glands enlarge to increase their PTH-secretory capacity.

19. What pathophysiologic changes occur in tertiary HPT?

Tertiary HPT usually progresses from secondary HPT when prolonged hyperphosphatemia and hypocalcemia cause autonomous parathyroid hyperplasia and hypercalcemia and is most common

TABLE 19.3 Hypercalcemia: PHPT and Malignancy

	Serum Levels			
	INTACT PTH	**PTHRP**	**1,25(OH)$_2$D**	**CALCIUM***
PHPT	↑ Normal	↓	↑	↑ Normal
PTHrP malignancy	↓	↑	↓ Normal	↑
Non-PTHrP malignancy	↓	↓	↓ Normal	↑

↑, Increased; ↓, decreased; *PHPT*, primary hyperparathyroidism; *PTHrP*, parathyroid hormone–related protein. *Calcium is usually high in PHPT, but calcium may be normal, and PTH is high in normocalcemic PHPT.

in advanced CKD. The changes from hypocalcemia to normocalcemia and, finally, hypercalcemia with marked increases in PTH mark the transition from secondary HPT to tertiary HPT. PTH levels are often >15 times the normal upper limit. Other findings include decreased parathyroid CaSR, VDR, and FGFR function and numbers. In tertiary HPT, PTH levels remain elevated despite vitamin D therapy and correction of hyperphosphatemia, and hypercalcemia persists despite the reduction or discontinuation of vitamin D and calcium supplements. Tertiary HPT usually requires resection of at least 3.5 parathyroid glands to correct the hypercalcemia. However, adjusting vitamin D analogs and phosphate binders and administering oral or intravenous (IV) calcimimetics, cinacalcet or etelcalcetide, may reduce PTH and calcium to acceptable ranges and delay or obviate surgery.

20. How is hypercalcemia in HHM distinguished from PHPT?

The main distinguishing features of HHM are the levels of intact PTH and PTHrP. Table 19.3 shows the classic and most common patterns of these hormones. Patients with PHPT usually have elevated PTH and low or low-normal PTHrP. In contrast, patients with malignancy-associated hypercalcemia have low PTH levels (<20 pg/mL). About 80% have increased PTHrP levels (PTHrP malignancy), and 20% have low PTHrP levels (non-PTHrP malignancy). Thus, measuring the two hormones distinguishes all three disorders (see question 21).

21. How do PTHrP and PTH differ?

PTHrP consists of three protein forms with 139, 141, and 173 amino acids. The first 139 amino acids are the same among the three forms. Eight of the first 13 N-terminal amino acids are identical to those of intact PTH (1–84), allowing PTHrP to bind to and stimulate the same receptors as PTH and to have similar hypercalcemic effects. However, the two hormones have different effects on 1,25(OH)2 vitamin D levels, partly because of their different secretion patterns. PTH (in PHPT) and PTHrP (in HHM) stimulate receptors that activate renal 1-alpha-hydroxylase. However, PTH secretion in PHPT is intermittent, whereas PTHrP secretion by malignant tumors is more continuous, which probably downregulates these receptors, inhibiting 1-alpha-hydroxylase activity and decreasing 1,25(OH)2 vitamin D production. A continuous infusion of PTH causes similar decreases in 1,25(OH)2 vitamin D. Other mechanisms may further decrease 1,25(OH)2 vitamin D in PTHrP-associated HHM. HHM may also be associated with a 5- to 10-fold increase in the phosphaturic factor FGF23, which inhibits 1-alpha-hydroxylase activity and decreases 1,25(OH)2 vitamin D levels. The higher calcium levels typically encountered in HHM may also decrease 1-alpha-hydroxylase activity and 1,25(OH)2 vitamin D levels.

22. What hormonal and mineral changes differentiate PHPT and HHM?

Primary hyperparathyroidism (PHPT) and hypercalcemia of malignancy (HHM) have key differences in hormone and mineral levels (see Table 19.3). Both conditions present with hypercalcemia that tends to be higher in HHM. PTH is high or high-normal in PHPT and low or low-normal in HHM. HHM is associated with high levels of parathyroid hormone-related protein (PTHrP), while PTHrP levels are low in PHPT. A unique difference between the two conditions is the level of 1,25(OH)$_2$ vitamin D. This hormone is typically elevated in PHPT and low or low-normal in HHM. In HHM, continuous production of PTHrP down regulates the 1-alpha-hydroxylase receptor, reducing 1,25(OH)$_2$ vitamin D production. In PHPT, intermittent secretion of PTH avoids this downregulation and increases 1,25(OH)$_2$ vitamin D production. Both conditions are associated with increased fibroblast growth factor 23 (FGF23) and decreased phosphorus levels. PHPT typically has associated hypophosphatemia, hyperchloremia, an increased chloride/phosphate ratio, and mild renal tubular acidosis, but these are not specific enough for diagnosis. However, the diagnosis of PHPT is more likely when there is hypercalcemia, elevated or high-normal PTH, low or low-normal phosphate, and elevated 1,25(OH)$_2$ vitamin D levels.

23. What PTH assay is most useful in the workup of hypercalcemia?

Intact PTH has 84 amino acids, with 70% metabolized by the liver and 20% metabolized by the kidneys; it has a half-life of 2 to 4 minutes. Less than 1% of the secreted intact hormone remains to interact physiologically with PTH receptors. Although the first 34 amino acids of the N-terminus contain the full biological activity of the hormone, intact PTH (1–84) is the active hormone in vivo. The usual PTH measured in most laboratories is a second-generation assay using two sets of capture antibodies to the carboxy-terminal (39–84 amino acids) and a signal antibody specific for the amino-terminal (1–34 amino acids). This detects the "intact" PTH hormone. A modification of this intact PTH assay is a quick or rapid assay used in the operating room. Rapid PTH ICMA measurements of intact PTH are performed preoperatively and intraoperatively (10–20 minutes after parathyroidectomy). A reduction in PTH of at least 50% indicates a successful operation.

In renal failure, non–(1–84) PTH fragments accumulate, with the main PTH-C fragment being PTH 7–84. PTH-C fragments cross-react with the intact PTH assays and increase the healthy reference range for PTH to 1.5–3 times the normal upper limit. A third-generation assay called a whole or intact PTH assay was developed to account for these molecules with signal antibodies to the 1- to 4–amino-terminal amino acids, proving to quantify intact PTH 1–84 more accurately. However, second- and third-generation assays are comparable in clinical medicine.

24. What methods best localize the parathyroid tumor in PHPT?

Parathyroid imaging techniques are expensive and are not used for diagnosis but as an aid for localizing parathyroid adenomas before and during parathyroid surgery.

Tc99m sestamibi single-photon emission CT/CT or sestamibi SPECT/CT is the first-line imaging technique for preoperative localization of parathyroid adenomas in patients with primary hyperparathyroidism (PHPT). Sestamibi SPECT/CT parathyroid scanning may be more than 85% to 90% sensitive, specific, and accurate for localizing parathyroid adenomas but is much less useful for parathyroid hyperplasia. The study couples a SPECT camera with CT in a single integrated unit that offers combined functional and anatomic localization of scintigraphic findings identified on the SPECT images. F18-choline (FCH) positron emission tomographic (PET)/computed tomographic (CT) (F18-choline PET/CT) is a newer and possibly more sensitive, specific, and accurate parathyroid adenoma-localizing technique that will become more available in the future and should be considered if standard sestamibi scanning does not identify the parathyroid adenoma. Ultrasonography is complementary to sestamibi or PET scanning and, when combined, often increases localization sensitivity >95%. It is also important to identify concomitant thyroid lesions that may require surgery.

Four-dimensional computed tomography (4D-CT) of the parathyroid, introduced in 2006, helps identify abnormal parathyroid glands and provides a fourth dimension with IV contrast enhancement of parathyroid adenomas on early-phase imaging and persistent hyperenhancement on delayed imaging after contrast administration. The degree of early enhancement and slow contrast washout correlates with the parathyroid adenoma metabolic activity. Thus, 4D-CT demonstrates function and detailed anatomy of parathyroid adenomas and surrounding structures. Combined sestamibi uptake and intraoperative gamma-probe localization assist localization for minimally invasive parathyroidectomy (see next question). Less commonly, localization studies include cervical CT, magnetic resonance imaging (MRI), intravenous digital subtraction angiography (IVDSA), arteriography, and selective venous sampling.

25. When should you use preoperative localization of a parathyroid adenoma?

It is standard of care to perform preoperative imaging to localize parathyroid tissue after deciding to proceed with parathyroidectomy. Parathyroid sestamibi scanning using SPECT-CT is a first-line, highly accurate imaging technique that, when combined with ultrasound and 4D CT, provides excellent localization and detailed 3D imaging of the parathyroid glands. This combined imaging approach can identify one or more overactive parathyroid glands and is highly sensitive and specific for identifying parathyroid and thyroid abnormalities. Preoperative imaging of the parathyroid glands and thyroid will often determine the type and extent of the surgery performed. The specific preoperative imaging will often depend on the surgeon's preference, and the surgeon may want to evaluate the patient and order the imaging studies according to preference. Patients undergoing parathyroidectomy should have preoperative thyroid ultrasonography because of the high rate of concomitant thyroid disease that may require resection. Minimally invasive parathyroidectomy (MIP) using a small incision localized to one side of the neck is becoming the state-of-the-art surgical approach to treating PHPT and always requires preoperative localization. Minimally invasive radio-guided parathyroidectomy (MIRP) uses radioactive sestamibi uptake with an intraoperative gamma probe that provides the least invasive and most accurate tumor localization. MIRP shortens the operative time, allows for an outpatient procedure with local anesthesia, enables precise localization of multiple adenomas, and allows some patient discharges within hours of the procedure. Standard neck exploration, MIP, and MIRP all require an experienced parathyroid surgeon. Most surgeons will require one or more imaging studies, summarized in question 24, before the operation.

26. Do all asymptomatic patients with PHPT require surgical treatment?

No. Many asymptomatic patients with mild PHPT do not require surgery (see question 27). However, the only definitive therapy for PHPT is parathyroidectomy, and it is usually appropriate to recommend parathyroidectomy for patients with asymptomatic PHPT if they have access to an experienced parathyroid surgeon and have no contraindications to surgery. The advantages of parathyroid surgery are a cure for PHPT and hypercalcemia in most cases with a single operation, no need for regular prolonged follow-up, decreased fracture rate, increased bone density, decreased frequency of kidney stones, and possible improvements in some neurocognitive elements.

27. What are the indications for parathyroidectomy in patients with asymptomatic PHPT?

In November 2022, members of the Fifth International Workshop on Evaluation and Management of Primary Hyperparathyroidism published guidelines for recommending parathyroid surgery in asymptomatic PHPT based on age, hypercalcemia, hypercalciuria, and kidney and bone health. The recommendations for parathyroidectomy include any of the following.

- Age <50 years.
- Hypercalcemia with serum calcium >1.0 mg/dL above the upper normal limit.
- Hypercalciuria with 24-hour urine calcium >300 mg in men, >250 mg in women, or increased stone risk by urinary stone risk profile.
- Hypercalcemia and hypercalciuria-related kidney abnormalities, including decreased estimated glomerular filtration rate (eGFR) to <60 mL/min and calcium nephrolithiasis or nephrocalcinosis by radiography, ultrasonography, or CT scan.
- PTH-related bone abnormalities, including decreased bone density at the lumbar spine, femoral neck, total hip, or distal one-third radius with DXA T-score ≤–2.5; a history of previous fragility fracture; and vertebral fracture (VF) by x-ray, CT, MRI, or vertebral fracture assessment (VFA).
- Patients for whom medical surveillance is neither desired nor possible.

28. How should you monitor and treat patients with asymptomatic PHPT who have not had parathyroidectomy?

Initially, obtain serum calcium, PTH, GFR, a 24-hour urine sample for calcium and creatinine, and imaging studies for kidneys and spine. Repeat calcium, PTH, and GFR tests yearly and other studies as necessary. Cortical bone loss occurs more frequently in PHPT, particularly in the distal radius and femoral neck. However, bone loss can happen anywhere in the body. So, to monitor bone loss, order a three-site dual-energy x-ray absorptiometry (DXA/BMD) study every 1–2 years. This study includes the distal forearm radius, femoral neck, total hip, and lumbar spine. PHPT increases total and vertebral fractures (VF), and one-third of VF are asymptomatic. Therefore ordering a vertebral fracture assessment (VFA) with the DXA study is important. Schedule office visits every 6–12 months and as needed to assess symptoms. Encourage hydration, exercise, and age-recommended calcium intake (diet + supplement) of 800 mg daily for women <50 and men <70 years old and 1000 mg daily for women >>50 and men >70 years old. Treat with vitamin D to ensure 25-OH vitamin D levels are 30–50 ng/mL. Treat with cinacalcet to lower serum calcium levels to normal and follow bone health guidelines to treat low BMD with bisphosphonates or denosumab to increase and stabilize BMD.

29. How would you estimate GFR without performing 24-hour urine collection?

Multiple equations exist for estimating GFR (eGFR) when kidney function is stable. Many laboratories provide an estimate of GFR when they measure creatinine on a multichannel laboratory test. Phone apps to estimate GFR are also available on Apple, Android, and Windows cell phones. The CKD-EPI creatinine equation for eGFR is the most accurate, and one can calculate it at https://www.kidney.org/professionals/KDOQI/gfr_calculator.

30. What therapeutic options are available for patients unable to undergo surgery for PHPT?

The U.S. Food and Drug Administration (FDA) has approved two calcimimetics that bind to the extracellular CaSRs on parathyroid cells and increase chief cell sensitivity to extracellular calcium. This effect shifts the calcium–PTH curve to the left. Cinacalcet is an oral calcimimetic that binds to the transmembrane domain of the CaSR and is approved to treat secondary HPT in patients with end-stage renal disease on dialysis, hypercalcemia in patients with parathyroid carcinoma, and PHPT in patients unable to undergo parathyroidectomy. Etelcalcetide, an IV calcimimetic, binds to the extracellular domain of the CaSR at a different site from calcium and is approved for treating secondary HPT in adults with CKD on hemodialysis. Both calcimimetics decrease serum calcium, PTH, and phosphorus levels. Etelcalcetide appears to be more effective. Bisphosphonates inhibit osteoclast-mediated bone resorption and can increase bone mass in patients with osteopenia and osteoporosis, as well as PHPT. Raloxifene may also preserve bone mass in patients who cannot tolerate bisphosphonates. Estrogens preserve bone mass, but their use remains controversial because of the associated potential risk of breast cancer and cardiovascular disease. Denosumab is a monoclonal antibody to receptor activator of nuclear factor-kappa B ligand (RANK-L) that decreases osteoclastic bone resorption and is FDA-approved to treat osteoporosis and hypercalcemia of malignancy. Angiographic ablation or percutaneous alcohol injection are rarely employed to treat a parathyroid adenoma. Emerging clinical studies demonstrate that thermal ablation techniques such as radiofrequency ablation (RFA) and microwave ablation (MWA) may be highly effective in treating parathyroid adenomas. These minimally invasive procedures are safe and provide a viable alternative to surgery for primary hyperparathyroidism (PHPT) and refractory secondary hyperparathyroidism (SHPT). The outcomes of these treatments are comparable to surgery without the added surgical risks but are only readily available in specialized treatment centers. Although more clinical experience and randomized controlled trials (RCTs) are needed, these methods could become the preferred treatment option for patients with parathyroid adenomas.

31. How would you evaluate and treat a patient with normocalcemic PHPT?

Normocalcemic PHPT (NCPHPT) manifests as elevated serum intact PTH levels with normal corrected and ionized calcium levels on two to three occasions over 3–6 months. Studies now suggest that NCPHPT may account for 1–4% of PHPT and can be associated with similar complications seen in hypercalcemic PHPT; however, the complications usually take longer to manifest. To diagnose NCPHPT, first evaluate and treat for all secondary causes of HPT, including vitamin D deficiency, CKD, calcium malabsorption, and renal leak hypercalciuria. Measure ionized calcium to confirm the normocalcemia. Correct any vitamin D deficiency to 25-OH vitamin D levels of 30–50 ng/mL. After ruling out secondary HPT, monitor and treat as for hypercalcemic HPT. However, referral for parathyroid surgery for NCPHPT patients should be based on an individualized assessment of symptoms and signs (see questions 27 and 28).

32. What should you consider in the patient described below 3 months after minimally invasive parathyroidectomy with persistently elevated PTH?

The patient is a 60-year-old Caucasian woman. She had elevated calcium levels for 2 years, averaging 11.2 mg/dL, and elevated PTH levels, averaging 95 pg/mL, before surgery. She underwent minimal parathyroidectomy that successfully removed a localized parathyroid adenoma. During surgery, her PTH levels decreased to 45 pg/mL and her calcium levels temporarily decreased to 8.2 mg/dL. Her calcium levels have remained normal at 9.0 to 9.5 mg/dL after 3 months, while her 25-OH vitamin D levels are 29 ng/mL, and her PTH levels have risen to 80 to 90 pg/mL. Even with successful parathyroid surgery and normal calcium levels, PTH levels may remain elevated in about 25% of patients for months. In this patient, the first consideration is a surgical cure with a delayed return of PTH to normal. Older patients, those with a longer duration of PHPT, higher preoperative PTH levels, lower 25-OH vitamin D levels, and CKD, are more likely to have prolonged PTH elevations after curative parathyroidectomy. The prolonged return of PTH to normal may be because of mild secondary hyperparathyroidism associated with bone remineralization. It is essential to correct low 25-OH vitamin D levels to 30–50 ng/mL and recommend calcium supplementation based on age and gender.

KEY POINTS

Hyperparathyroidism

- Primary hyperparathyroidism (PHPT) is associated with elevated PTH, hypercalcemia, osteoporosis, nephrolithiasis, and symptoms associated with these conditions.
- Reasons for recommending surgery for patients with asymptomatic PHPT include any of the following: age <50 years, serum calcium >1.0 mg/dL above the normal upper limit; decreased estimated glomerular filtration rate (GFR) <60 mL/min, calcium nephrolithiasis or nephrocalcinosis; 24-hr urine calcium >300 mg in men and >250 mg women, and increased stone risk by urine biochemical analysis; reduced bone mineral density at the spine, hip, or distal one-third radius with T-score <-2.5; fragility fracture; vertebral compression fracture or increased risk of vertebral fracture (VF) by VFA.
- It is always appropriate to recommend surgery to treat asymptomatic PHPT if the patient has no contraindications for surgery and has access to a skilled parathyroid surgeon.
- Advantages of parathyroid surgery include cure of PHPT and hypercalcemia in most cases with a single operation, no need for regular prolonged follow-up, increased bone density, decreased fracture rate, decreased kidney stone formation, increased quality of life, and potentially improved neurocognitive function.
- Although neurocognitive, neuropsychiatric, gastrointestinal, and musculoskeletal symptoms may improve after surgery, these symptoms are not specific indications for parathyroidectomy.
- Parathyroid imaging is expensive and not usually used to confirm or exclude the diagnosis of PHPT. However, preoperative parathyroid localization studies are the norm, and thyroid ultrasonography to screen for thyroid disease is also usually done before parathyroid surgery. Cervical ultrasonography performed by an experienced parathyroid sonographer is the least costly imaging modality and when combined with Tc99m sestamibi SPECT-CT and 4D-CT, is the most effective localization strategy.

WEBSITES

Parathyroid.com (good review of all aspects of parathyroid disease): http://www.parathyroid.com.

Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop (endocrinology.org)

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Hypercalcemia of Malignancy

Michael T. McDermott

1. What are the three major types of hypercalcemia of malignancy?

Humoral Hypercalcemia of Malignancy (HHM): Parathyroid hormone related peptide (PTHrP) is the most common mediator of HHM. PTHrP promotes both osteoclastic bone resorption and calcium reabsorption in the distal renal tubules. Humoral mediators that can also cause HHM include transforming growth factor alpha (TGFα) and tumor necrosis factor (TNF). HHM accounts for about 80% of all hypercalcemia of malignancy.

Local Osteolytic Hypercalcemia (LOH): Cytokine production within bone metastases causes LOH. Cytokines stimulate aggressive local bone resorption and calcium release at metastatic sites. LOH accounts for about 20% of all hypercalcemia of malignancy.

Calcitriol Mediated Hypercalcemia: Calcitriol (1,25 dihydroxy-vitamin D) production by a tumor promotes hypercalcemia by both increased intestinal calcium absorption and excessive osteoclastic bone resorption. This condition accounts for approximately 1% of all hypercalcemia of malignancy.

2. What is parathyroid hormone related peptide (PTHRP)?

Parathyroid hormone related peptide (PTHrP) has sequence homology with the first 13 amino acids of parathyroid hormone (PTH). Both PTH and PTHrp bind to the common PTH/PTHrp receptor, resulting in stimulation of bone resorption and inhibition of renal calcium excretion. PTHrp is found in high concentrations in breast milk and amniotic fluid and is increased in the circulation during pregnancy. Its physiologic endocrine function may be to govern the transfer of calcium from the maternal skeleton and bloodstream into the developing fetus and into breast milk. PTHrP produced by tumors is by far the most common humoral mediator of HHM.

3. What types of cancer most commonly cause HHM?

Lung cancer, particularly squamous cell carcinoma, is the most common malignancy causing HHM. Other tumors associated with HHM include squamous cell carcinomas of the head and neck and esophagus and adenocarcinomas of the breast, kidney, bladder, pancreas, and ovary. Non-Hodgkin's lymphoma and chronic myelogenous leukemia can also cause HHM.

4. What types of cancer are associated with LOH?

Breast cancer with skeletal metastases, multiple myeloma, and lymphoma are the major cancers associated with LOH. These metastatic and primary bone tumors secrete cytokines directly into bone where they stimulate aggressive local bone resorption. Local cytokines that have been identified or proposed in LOH include PTHrP, DKK1, lymphotoxin, interleukins, transforming growth factors, prostaglandins, and procathepsin D.

5. What types of cancer cause calcitriol mediated hypercalcemia and how does this happen?

Lymphomas are the most common malignancies that cause hypercalcemia due to excess production of 1,25$(OH)_2$ Vitamin D (calcitriol). However, the most common overall cause of this is sarcoidosis. In these conditions, lymphomas or granulomatous tissues express high levels of 1 alpha hydroxylase, the enzyme that converts 25(OH) Vitamin D into 1,25$(OH)_2$ Vitamin D, the active form of the vitamin that stimulates intestinal absorption of calcium and phosphorus.

6. What are the key diagnostic features of the three types of hypercalcemia of malignancy?

See Table 20.1.

TABLE 20.1 Differential Diagnosis of Hypercalcemia of Malignancy—Useful Lab Tests

	PTH	PTHrP	1,25 (OH)$_2$ VITAMIN D
Humoral Hypercalcemia of Malignancy	↓	↑	↓or Normal
Local Osteolytic Hypercalcemia	↓	↓	↓or Normal
Calcitriol Mediated Hypercalcemia*	↓	↓	↑

**Note*: The most common overall cause of calcitriol mediated hypercalcemia is sarcoidosis.

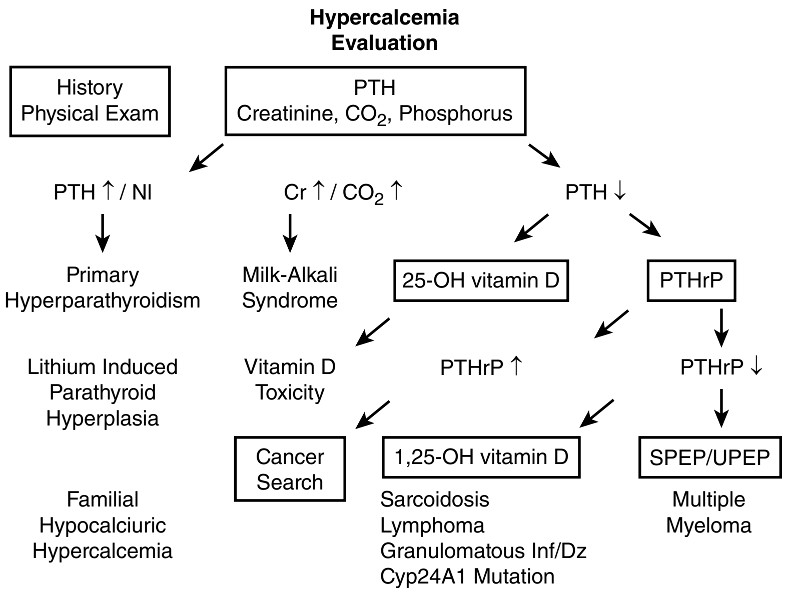
Hypercalcemia Evaluation
History
Physical Exam
PTH
Creatinine, CO2, Phosphorus
PTH ↑ / Nl
Cr ↑ / CO2 ↑
PTH ↓
Primary Hyperparathyroidism
Milk-Alkali Syndrome
25-OH vitamin D
PTHrP
Lithium Induced Parathyroid Hyperplasia
Vitamin D Toxicity
PTHrP ↑
PTHrP ↓
Cancer Search
1,25-OH vitamin D
SPEP/UPEP
Familial Hypocalciuric Hypercalcemia
Sarcoidosis
Lymphoma
Granulomatous Inf/Dz
Cyp24A1 Mutation
Multiple Myeloma

Fig. 20.1 Diagnostic approach to the patient with hypercalcemia.

7. What is a good general diagnostic approach for a patient with hypercalcemia of unknown cause?

Evaluation of hypercalcemia should always start with a good history and physical examination and measurement of PTH, creatinine, CO_2, and phosphorus. When the serum PTH is low, one must have a high degree of suspicion for hypercalcemia of malignancy. A good diagnostic approach to hypercalcemia is shown in Fig. 20.1.

8. What is the definition of a hypercalcemic crisis?

Hypercalcemic crisis is defined as a serum calcium level >14 mg/dl with associated symptoms. The symptoms and features most commonly seen with serum calcium levels this high include nausea, vomiting, dehydration, mental status changes, acute kidney injury, electrocardiographic (ECG) changes, and cardiac dysrhythmias.

9. What ECG changes are characteristic of severe hypercalcemia?

A shortened QTC is a classic ECG finding of severe hypercalcemia (hypocalcemia causes a prolonged QTC). Other changes that may be seen include first degree heart block, scooped ST elevations in leads V1-V5, and scooped ST depressions in the inferior leads.

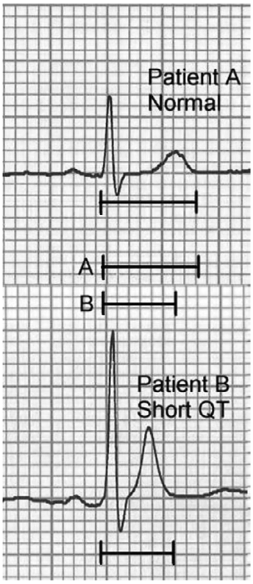

Fig. 20.2 Shortened QTC (patient B) is a characteristic feature of a hypercalcemic crisis.

TABLE 20.2 Treatment of Specific Types of Hypercalcemia of Malignancy

PTHrP/Cytokine Mediated Hypercalcemia of Malignancy (HHM, LOC, Myeloma) Saline Infusion: 200–300 ml/hour to keep urine output approximately 100–150 ml/hour Calcitonin: 4 IU/kg SQ or IM; repeat 4–8 IU/kg every 6–12 hours for 48 hours Zoledronic Acid (Zometa): 4 mg IV over 15 minutes (30–60 minutes in CKD) Denosumab (Xgeva): 120 mg SQ Dialysis: if refractory to the above measures
Calcitriol [1,25 (OH_2) Vitamin D] Mediated Hypercalcemia of Malignancy Glucocorticoids: Prednisone 60 mg daily for 10 days Saline Infusion: 200–300 ml/hour to keep urine output approximately 100–150 ml/hour Calcitonin: 4 IU/kg SQ or IM; repeat 4–8 IU/kg every 6–12 hours for 48 hours Zoledronic Acid (Zometa): 4 mg IV over 15 minutes (30–60 minutes in CKD) Denosumab (Xgeva): 120 mg SQ Dialysis: if refractory to the above measures

IV, intravenous; *IM*, intramuscular; *SQ*, subcutaneous

10. Describe appropriate treatment approaches for the different types of hypercalcemia of malignancy.

Treatment of the primary malignancy is the most important long-term measure. To lower serum calcium levels to a safe range quickly and effectively, one must first attempt to determine the underlying mechanism and malignancy causing the hypercalcemia. Table 20.2 lists the measures that can be used selectively for treatment of the specific type of hypercalcemia.

11. What is the prognosis for patients with hypercalcemia of malignancy?

Because hypercalcemia often (but not always) correlates with advanced malignancy and metastatic disease, the overall prognosis is generally quite poor. In one study, the median survival of patients who developed hypercalcemia was only 30 days. However, this varies significantly depending on the primary tumor/malignancy and the response to antitumor therapy. Collaboration with the oncology providers and shared decision-making with the patient and family should guide realistic further diagnostic and therapeutic considerations. However, never underestimate your patient’s will to defeat their malignancy and to survive.

KEY POINTS

Hypercalcemia of Malignancy

- Humoral hypercalcemia of malignancy (HMM) usually results from solid tumor production of parathyroid hormone–related peptide (PTHrp), which binds to parathyroid hormone (PTH) and PTH/PTHrp receptors to stimulate bone resorption and renal tubular calcium reabsorption.
- Local osteolytic hypercalcemia (LOH) is caused by skeletal metastases that secrete cytokines directly into bone, stimulating aggressive localized bone resorption and calcium release.
- Calcitriol mediated hypercalcemia occurs when marrow/hematologic malignancies express 1 alpha hydroxylase, resulting in production of high levels of $1,25(OH)_2$ Vitamin D.
- The key initial diagnostic test for hypercalcemia is serum PTH measurement; PTH is elevated or high normal in primary hyperparathyroidism (most common cause of hypercalcemia) but low or undetectable in hypercalcemia of malignancy.
- Serum calcium levels can be lowered effectively in people with hypercalcemia of malignancy by the intravenous administration of saline and parenteral calcitonin, bisphosphonates or denosumab.
- The development of hypercalcemia of malignancy portends a poor prognosis in most cancer patients because it tends to occur with advanced tumor stages.

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Hypocalcemia

Shari C. Fox

1. Define hypocalcemia.

Hypocalcemia is the state in which the serum ionized calcium level drops below the normal range, which, under normal conditions, corresponds to a serum total calcium level <8.5 mg/dL (2.1 mmol/L).

2. How are serum calcium and serum albumin levels related?

Approximately 50% of serum calcium is bound to albumin, to other plasma proteins, and to related anions such as citrate, lactate, and sulfate. Of this, 40% is bound to protein, predominantly albumin, and 10% to 13% is attached to anions. The remaining 50% is unbound or ionized calcium. The total serum calcium level reflects both the bound and the unbound portions with a normal range of 8.5 to 10.5 mg/dL for most assays (2.1–2.5 mmol/L).

3. How is the serum total calcium corrected for a low serum albumin level?

Serum total corrected calcium is calculated by the addition of 0.8 mg/dL (0.2 mmol/L) to the measured serum total calcium for every 1 g/dL that the serum albumin is below 4 g/dL. This is not a completely precise method, and therefore serum ionized calcium measurements may be needed to confirm whether true hypocalcemia is present. The adjusted level of serum total calcium correlates with the ionized calcium level, which is the physiologically active form of serum calcium.

4. What is the most common cause of low total serum calcium?

Hypoalbuminemia is the most common cause of low total serum calcium. In patients with chronic illness, malnutrition, cirrhosis, or volume overexpansion, serum albumin may be low, and this will reduce the total but generally not the ionized fraction of serum calcium. This could be thought of as "factitious" hypocalcemia.

5. What factors other than albumin influence the levels of serum ionized calcium?

Serum pH influences the level of ionized calcium by causing decreased binding of calcium to albumin in acidosis and increased binding in alkalosis. As an example, respiratory alkalosis, seen in hyperventilation, causes a drop in the serum ionized calcium level. A shift of 0.1 pH units is associated with an ionized calcium change of 0.16 to 0.20 mg/dL (0.04–0.05 mmol/L). Increased levels of chelators, such as citrate, which may occur during large-volume transfusions of citrate-containing blood products, also may lower the levels of ionized calcium. Heparin may act similarly.

6. How is serum calcium regulated?

Calcium homeostasis is maintained within a narrow range in normal individuals by the interplay of parathyroid hormone (PTH), vitamin D, calcitonin and fibroblast growth factor 23 (FGF23). PTH acts in three ways to raise serum calcium levels: (1) PTH stimulates osteoclastic bone resorption; (2) PTH increases conversion of 25-hydroxy (OH) vitamin D to 1,25-dihydroxy (OH_2) vitamin D, which then increases intestinal calcium and phosphorus absorption; and (3) PTH increases renal reabsorption of calcium. Calcitonin decreases the level of serum calcium by suppressing osteoclast activity in bone. FGF23 (fibroblast growth factor) inhibits conversion of 25-hydroxy (OH) vitamin D to its active form, 1,25-dihydroxy (OH_2) vitamin D. Calcium can also be impacted by phosphate and magnesium levels.

7. What steps in vitamin D metabolism may influence serum calcium levels?

Vitamin D is obtained through the diet or is formed in the skin in the presence of ultraviolet light. Vitamin D is converted to 25-OH vitamin D in the liver and finally to 1,25-dihydroxy $(OH)_2$ vitamin D, the most active form of vitamin D, in the kidney. 1,25$(OH)_2$ vitamin D acts directly on intestinal cells to increase calcium and phosphorus absorption. Deficiency in any of these steps may cause hypocalcemia.

8. What are the major causes of 'true' hypocalcemia?

Among all the causes of hypocalcemia, postsurgical hypoparathyroidism, vitamin D deficiency, and autoimmune hypoparathyroidism are the most common. The multiple organ and hormonal regulatory systems involved in calcium homeostasis, however, create the potential for multiple causes of hypocalcemia. The etiology of hypocalcemia must be considered in relation to the level of serum albumin, the secretion of PTH, the level of vitamin D, and the presence or absence of hyperphosphatemia. Initially, hypocalcemia may be approached by a search for failure in one or more of these systems. The systems primarily involved are the parathyroid glands, bone, kidney, and liver; the following list shows the clinical entities followed by their mechanisms:

- *Hypoparathyroidism:* decreased PTH production
- *Hypomagnesemia:* decreased PTH release, responsiveness, and action
- *Citrate toxicity from massive blood transfusions:* complexing of calcium with citrate
- *Pseudohypoparathyroidism:* PTH ineffective at target organs
- *Liver disease:* decreased albumin production, decreased 25-OH vitamin D production, drugs that stimulate 25-OH vitamin D metabolism
- *Renal disease:* renal calcium leak, decreased $1{,}25(OH)_2$ vitamin D production, elevated serum phosphate (PO_4) from decreased PO_4 clearance; drugs that increase renal clearance of calcium
- *Bone disease:* drugs suppressing bone resorption; "hungry bone syndrome"—recovery from hyperparathyroidism or hyperthyroidism
- *Phosphate load:* endogenous—tumor lysis syndrome, hemolysis, and rhabdomyolysis; exogenous—phosphate-containing enemas, laxatives, and phosphorus burns
- *Pancreatitis:* sequestration/deposition of calcium in the pancreas; other
- *Toxic shock syndrome, other critical illnesses:* decreased PTH production or PTH resistance

9. What physical signs suggest hypocalcemia?

The hallmark of acute hypocalcemia is tetany, which is characterized by neuromuscular irritability. The tetany can be mild or more severe and is usually seen when the serum ionized calcium concentration is <4.3 mg/dL (total serum calcium <7.0–7.5 mg/dL). In addition to neuromuscular irritability, some patients have less specific symptoms such as fatigue, anxiety, depression, and hyperirritability.

- *Mild tetany:* perioral numbness, paresthesias of hands/feet, and muscle cramps
- *Severe tetany:* carpopedal spasms, laryngospasm, and focal or generalized seizures
- *Latent tetany:* Trousseau's and Chvostek's signs

Chvostek's sign is an ipsilateral facial twitch elicited by tapping the skin over the facial nerve anterior to the external auditory meatus. Chvostek's sign is also present in 10% of normal individuals. Trousseau's sign is a forearm spasm induced by inflation of a blood pressure cuff to 20 mm Hg above the patient's systolic blood pressure for 3 to 5 minutes. Carpal spasm presents as flexion of the wrist and metacarpophalangeal joints, extension of the fingers, and adduction of the thumb.

10. What laboratory tests are clinically useful in distinguishing among the causes of hypocalcemia?

Table 21.1 summarizes the laboratory findings for common causes of hypocalcemia. Besides intact PTH and corrected (or ionized) calcium in serum, which are the most important initial tests, other tests that can be helpful depending on the clinical presentation and history include serum creatinine, phosphate, magnesium, vitamin D metabolites, alkaline phosphatase, amylase, and urinary calcium and magnesium.

11. Describe the symptoms of hypocalcemia.

- *Early symptoms:* numbness and tingling involving fingers, toes, and lips
- *Neuromuscular symptoms:* cramps, fasciculations, laryngospasm, and tetany
- *Cardiovascular symptoms:* arrhythmias, bradycardia, and hypotension
- *Central nervous system symptoms:* irritability, paranoia, depression, psychosis, organic brain syndrome, and seizures; "cerebral tetany," which is not a true seizure (see Question 13), may also be seen in hypocalcemia; subnormal intelligence has also been reported

TABLE 21.1 Differential Diagnosis of Laboratory Evaluation of Most Common Causes of Hypocalcemia

	CALCIUM (SERUM CORRECTED)	PTH	25-OH VITAMIN D	1,25-OH VITAMIN D	MAGNESIUM	PHOSPHORUS	CREATINE
Hypoparathyroidism	↓	↓	Nl	↓	Nl	↑	Nl
Pseudohypoparathyroidism (PTH resistance)	↓	↑	Nl	↓ or Nl	Nl	↑	Nl
Liver disease	↓	↑	↓	↓ or Nl		↓	Nl
Hypomagnesemia	↓	↓ or Nl	Nl	Nl	↓	Nl	Nl
Vitamin D deficiency	↓	↑	↓ or Nl	↓ or Nl or ↑	Nl	↓ or Nl	↓ or Nl
Renal disease (secondary hyperparathyroidism)	↓	↑	Nl	↓ or Nl	↑ or Nl	↑	↑

↑, Increased; ↓, decreased; *Nl*, normal; *PTH*, parathyroid hormone.

- *Chronic symptoms:* papilledema, basal ganglia calcifications, cataracts, dry skin, coarse hair, and brittle nails

Symptoms reflect the absolute calcium concentration and the rate of fall in the calcium levels. Individuals may be unaware of symptoms because of gradual onset and may realize they have experienced an abnormality only when their sense of well-being improves with treatment.

12. What radiographic findings may be present with hypocalcemia?

Calcifications of basal ganglia may occur in the small blood vessels of that region. These occasionally may cause extrapyramidal signs but usually are asymptomatic. Of note, 0.7% of routine brain computed tomography (CT) scans show calcification of the basal ganglia.

13. What is cerebral tetany, and how does it differ from a true seizure?

Cerebral tetany manifests as generalized tetany without loss of consciousness, tongue biting, incontinence, or postictal confusion. Anticonvulsants may relieve the symptoms, but because they enhance 25-OH vitamin D catabolism, they also may worsen hypocalcemia.

14. How does hypocalcemia affect cardiac function?

Calcium is involved in cardiac automaticity and is required for muscle contraction. Hypocalcemia can, therefore, result in arrhythmias and reduced myocardial contractility. This decrease in the force of contraction may be refractory to pressor agents, especially those that involve calcium in their mechanism of action. Through this process, beta-blockers and calcium channel blockers can exacerbate cardiac failure. With low serum calcium, the QT interval is prolonged, and ST changes may mimic those seen in ischemia. Although the relationship is variable, the calcium level inversely correlates moderately well with the interval from the Q-wave onset to the peak of the T wave. NOTE: if serum ionized calcium is low, one should consider ordering an EKG to look for QT prolongation; if present, given the risk for torsades de pointes, more urgent treatment of hypocalcemia may be indicated.

15. What are the potential ophthalmologic findings in hypocalcemia?

Papilledema may occur with subacute and chronic hypocalcemia. This is most often asymptomatic and usually resolves with normalization of the serum calcium level. If symptoms develop or if papilledema does not resolve when the calcium level is normalized, a cerebral tumor and benign intracranial hypertension must be excluded. Optic neuritis with unilateral loss of vision occasionally develops in people with hypocalcemia. Lenticular cataracts may also occur with long-standing hypocalcemia but usually do not change in size after hypocalcemia is corrected.

16. With which autoimmune disorders is hypocalcemia sometimes associated?

Hypoparathyroidism may result from autoimmune destruction of the parathyroid glands. This disorder has been associated with adrenal, gonadal, and thyroid failure, as well as with alopecia areata, vitiligo, and chronic mucocutaneous candidiasis. This combination of conditions, each associated with organ-specific autoantibodies, has been termed the *autoimmune polyendocrinopathy syndrome, type 1* (see Chapter 59).

17. Hypocalcemia is frequently encountered in intensive care settings. What are the potential causes?

Low total serum calcium levels, which are found in 70% to 90% of patients receiving intensive care, result from multiple causes, including:

- Hypoalbuminemia
- Hypomagnesemia
- Hyperphosphatemia
- Anticoagulant therapy
- Rapid blood transfusions with citrate as a preservative
- Administration of anionic loads causing chelation (i.e., citrate, lactate, bicarbonate, phosphate, oxalate, ethylenediaminetetraacetic [EDTA] acid, and radiographic contrast media)
- Parathyroid failure and decreased vitamin D synthesis in severe illness
- Sepsis inducing some degree of resistance to the biologic effects of PTH

Because of all the factors listed above, it is recommended that ionized serum calcium, rather than total serum calcium, be measured in patients with severe illness.

18. Hypocalcemia is not unusual in people with cancer. What conditions may lead to hypocalcemia in these individuals?

- Tumor lysis syndrome causes hyperphosphatemia and associated formation of intravascular and tissue calcium-phosphate complexes with resultant hypocalcemia.
- Multiple chemotherapeutic agents and antibiotics (amphotericin B and aminoglycosides) induce hypomagnesemia, which, in turn, impairs secretion of PTH and causes resistance to PTH in skeletal tissue.
- Thyroid surgery and neck irradiation with transient or permanent hypoparathyroidism may cause hypocalcemia.
- Medullary carcinoma of the thyroid and pheochromocytomas may secrete calcitonin and, on rare occasions, this causes hypocalcemia.

19. What drugs may cause hypocalcemia?

Phenobarbital, phenytoin, primidone, rifampin, and glutethimide increase hepatic metabolism of 25-OH vitamin D and thereby may cause hypocalcemia. Aminoglycosides, diuretics (furosemide), and chemotherapeutic agents that induce renal magnesium wasting, and laxatives or enemas that create a large phosphate load, also may be associated with hypocalcemia. Heparin, ketoconazole, isoniazid, fluoride, foscarnet, and glucagon may also induce hypocalcemia by a variety of mechanisms. Osteoporosis treatments, such as bisphosphonates (especially the more potent ones, i.e., zoledronic acid) and denosumab, inhibit osteoclast function and lower serum calcium levels, as does cinacalcet (a calcimimetic drug), which can acutely inhibit PTH release and lead to significant hypocalcemia in approximately 5% of treated individuals.

20. Which vitamin D metabolite is best for assessing total body vitamin D stores, 25-OH vitamin D or 1,25(OH)$_2$ vitamin D?

The serum 25-OH vitamin D level best reflects total body vitamin D stores. The conversion of 25-OH vitamin D to 1,25(OH)$_2$ vitamin D is tightly controlled, and the level of serum 1,25(OH)$_2$ vitamin D is usually maintained despite significant vitamin D depletion. Increases in PTH (primary or secondary hyperparathyroidism) stimulate increased conversion of 25-OH vitamin D to 1,25(OH)$_2$ vitamin D in this situation.

21. How is hypocalcemia treated?

Asymptomatic hypocalcemia requires supplementation with oral calcium and vitamin D derivatives to maintain serum calcium levels at least in the 7.5 to 8.5 mg/dL range. When the serum calcium falls acutely to a level at which the patient is symptomatic OR has a prolonged QT interval on EKG, intravenous calcium administration is recommended. The dosage of calcium depends on the amount of elemental calcium present in each preparation (Table 21.2). For a hypocalcemic emergency, 90 mg or 180 mg of calcium gluconate in 50 mL of dextrose 5% (D5) or normal saline (NS) may be given as an intravenous bolus over 10 to 20 minutes. This dose will only temporarily raise the serum calcium (i.e., for 2–3 hours) and must, therefore, be followed by a slow infusion of 0.5 to 2.0 mg/kg/hr of either calcium gluconate or calcium chloride (calcium gluconate is preferred because it is less likely to lead to tissue necrosis if extravasated).

22. When is treatment with 1,25(OH)$_2$ vitamin D (calcitriol) indicated?

Under normal conditions, 25-OH vitamin D is converted to 1,25(OH)$_2$ vitamin D (calcitriol) in the kidney through the stimulatory influence of PTH. Two conditions can, therefore, render the body unable to produce adequate amounts of calcitriol—hypoparathyroidism and renal failure. Because calcitriol is essential for normal intestinal calcium absorption, oral calcitriol (Rocaltrol) supplementation is indicated in patients who have either hypoparathyroidism or chronic renal failure. Of note, because vitamin D has weak biologic activity, these patients may be given large dosages of vitamin D (50,000–100,000 U/day) if calcitriol is unavailable.

TABLE 21.2 Elemental Calcium Content of Commonly Used Preparations

PREPARATION	ORAL DOSE	ELEMENTAL CALCIUM (mg)
Calcium Citrate		
Citracal	950 mg	200
Calcium Acetate		
PhosLo	667 mg	169
Calcium Carbonate		
Tums	500 mg	200
Tums Ex	750 mg	300
Oscal	625 mg	250
Oscal 500	1250 mg	500
Calcium 600	1500 mg	600
Titralac (suspension)	1000 mg/5 mL	400
INTRAVENOUS AGENTS	**VOLUME**	**ELEMENTAL CALCIUM (mg)**
Calcium chloride	2.5 mL of 10% solution	90
Calcium gluconate	10 mL of 10% solution	90
Calcium gluceptate	5 mL of 22% solution	90

23. What role can thiazide diuretics play in the treatment of hypocalcemia?

Thiazide diuretics reduce urinary calcium excretion significantly, especially with 24-hour coverage (hydrochlorothiazide twice daily or chlorthalidone once daily). These medications can be used to reduce urinary calcium losses and increase serum calcium levels mildly in patients with hypocalcemia caused by conditions that are associated with increased urinary calcium excretion (hypoparathyroidism and idiopathic hypercalciuria).

24. Can PTH be administered in the treatment of hypocalcemia due to hypoparathyroidism?

Once-daily subcutaneous injection of palopegteriparatide, a parathyroid hormone analog prodrug containing an inert carrier of teriparatide, provides parathyroid hormone (1-34) continuously and was approved by the FDA 8-2024. It can be considered in the treatment of patients with difficult-to-control hypocalcemia despite other available treatments options.

KEY POINTS

Hypocalcemia

- Serum calcium levels must be corrected for serum albumin levels for accurate assessment.
- Tetany and QT interval prolongation are hallmark features of acute hypocalcemia.
- Multiple organ systems, minerals, anions, and drugs affect calcium levels and must be considered in the evaluation of hypocalcemia.
- Hypocalcemia is a frequent problem in trauma and intensive care settings, and is often a result of administration of intravenous agents.
- Hypocalcemia with severe symptoms requires rapid correction with IV calcium therapy.
- Asymptomatic hypocalcemia can initially be treated with oral calcium alone.
- Calcium plus active 1,25-dihydroxy vitamin D (e.g., calcitriol) is the initial treatment of hypocalcemia in patients with hypoparathyroidism and renal failure.

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CHAPTER 22

Nephrolithiasis

Leonard R. Sanders

1. How would you define hypercalciuria, kidney (renal) stones, renal calculi, nephrolithiasis, urolithiasis, renal lithiasis, and nephrocalcinosis?

Hypercalciuria is urinary calcium excretion >300 mg/day in men and >250 mg/day in women. Another definition of hypercalciuria is urinary calcium excretion >4 mg/kg of ideal body weight per day in any gender. A 24-hour urine collection is required to diagnose hypercalciuria. The calcium-to-creatinine (Ca/Cr) ratio on a random or spot urine specimen estimates 24-hour calcium excretion. For example, if urine calcium is 20 mg/dL and urine creatinine is 70 mg/dL, the Ca/Cr ratio would be 20:70 or 0.286 g (286 mg/day). The estimated 24-hour urinary calcium excretion would be 286 mg/day. Despite the convenience of the Ca/Cr ratio, its accuracy can vary. Therefore the 24-hour urine collection remains the preferred method for an accurate diagnosis. Random urine samples, while easier for patients, are typically used for monitoring trends rather than for initial diagnosis. The first-morning voided urine is considered the most accurate for random samples. Kidney stones, renal calculi, nephrolithiasis, urolithiasis, and renal lithiasis are synonymous terms that define the clinical syndrome of formation and movement of stones in the urinary collecting system. Renal calculi are abnormally hard, crystalline, insoluble substances that form specifically in the renal collecting system. Nephrocalcinosis is the deposition of calcium salts in the renal parenchyma and tubules and may lead to acute kidney injury and kidney stones.

2. Who is at risk for the development of kidney stones?

Kidney stones affect 12% of the world's population. The average prevalence of kidney stones in the United States has increased and is approximately 11% in men and 7% in women, with an overall prevalence of 9%. The lifetime risk for kidney stones is 19% in men and 9% in women. The yearly cost of kidney stone disease in the United States is more than $5.5 billion. Fifty percent of patients with kidney stones have a recurrence within 5 to 10 years. Stones occur most often between 30 and 60 years of age and occur more often in Caucasians than in other ethnicities. Women have had more stones in recent years, possibly related to increased age, fast food consumption (high in protein and salt), increased calories, decreased physical activity, and increased obesity. The Women's Health Initiative data suggest that estrogen hormone replacement therapy increases the risk of nephrolithiasis in healthy postmenopausal women. Risks for stones include a family history of stones, sedentary lifestyle, obesity, diabetes mellitus, metabolic syndrome, hypertension, autosomal dominant polycystic kidney disease, medullary sponge kidney, renal tubular acidosis, urine volume <2 L/day, dietary calcium <1000 mg/day, dietary sodium >2 g/day, low water intake, high animal protein, and high intake of sugar-sweetened sodas (see question 4). A hot environment and global warming predispose to dehydration and kidney stones. Consider using the ROKS (Recurrence of Kidney Stone) calculator to predict the risk of stone recurrence.

3. What are the composition and frequency of kidney stones in the United States?

There are six major types of stones, as outlined in Fig. 22.1**,** which also shows the approximate frequency of occurrence of each type of stone.

4. What are the leading causes of nephrolithiasis?

The most common causes of nephrolithiasis are the various types of polygenic idiopathic hypercalciuria (IH): absorptive hypercalciuria (AH) types AH-I to AH-III (renal phosphate leak) and renal hypercalciuria (RH). Other causes are primary hyperparathyroidism and other causes of hypercalcemia, hyperoxaluria, hyperuricosuria, hyperphosphaturia, hypocitraturia, hypomagnesuria, infection stones, gouty diathesis, renal tubular acidosis, cystinuria, calcifying nanoparticles, monosodium urate, and alterations in the microbiome such as with antibiotics. Medications may rarely cause kidney stones, such as xanthine, triamterene, methotrexate, ephedrine, guaifenesin,

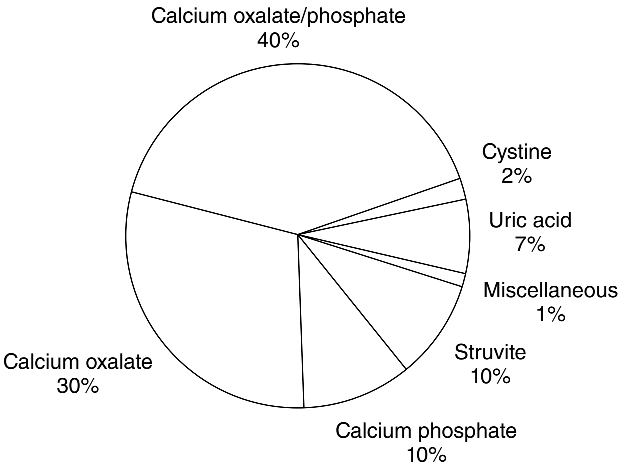

Fig. 22.1 Frequency of the types of kidney stones.

ciprofloxacin, and sulfonamides, and more commonly from protease inhibitors indinavir, atazanavir, and darunavir. Patients with idiopathic nephrolithiasis make up 10% to 20% of "stone formers" in whom routine workup yields no identifiable cause.

5. What conditions are associated with both renal stone disease and hypercalciuria?

Calcium stones account for 80% of all kidney stones. Approximately 40% to 50% of calcium stone formers have hypercalciuria. Of those with hypercalciuria, 40% have IH, 5% have primary hyperparathyroidism, and 3% have renal tubular acidosis. Other causes of hypercalciuria include excessive dietary vitamin D, excessive calcium and alkali intake, sarcoidosis, Cushing's syndrome, hyperthyroidism, Paget's disease of bone, and immobilization. Nephrolithiasis is also associated with infection, acute and chronic kidney injury, coronary artery disease, obesity, type 2 diabetes mellitus, hypertension, and metabolic syndrome. Lithogenic urine that includes urinary calcium >250 mg/d in women and >300 mg/d in men, oxalate >40 mg/d, uric acid >750 mg/d in women and >800 mg/d in men, citrate <325 mg/d, and urine volume <2 L/d is a strong risk factor for renal stone disease.

6. What are the most important causes of normocalciuric calcium nephrolithiasis?

The most important and most common causes of normocalciuric calcium nephrolithiasis are hypocitraturia (50%), hyperuricosuria (25%), hyperoxaluria (10%), and urinary stasis (5%).

7. What is the process of renal stone formation?

Renal stone formation occurs in six steps: (1) Initially, urinary crystallization or precipitation of sparingly soluble salts and acids occurs. (2) Nucleation follows as crystals and urinary matrix ions form a stable framework for crystal enlargement through, (3) growth, and (4) aggregation. After the crystals sufficiently enlarge, they become trapped and (5) retained in a narrow portion of the urinary collecting system at the end of the collecting ducts and near the renal papilla. Unless washed away by increased urinary flow, these aggregated crystals formed in the medullary interstitium are extruded and (6) adhere to the renal papillae to form a calcium phosphate–based Randall's plaque nidus for further crystal accumulation and stone growth. Once stone growth occurs, the stone may detach from the renal papilla, move distally, and cause obstruction. Common sites for obstruction are the ureteropelvic junction (UPJ), mid-ureter (where it crosses over the iliac artery), and ureterovesical junction (UVJ).

8. What pathophysiologic factors influence the formation of renal stones?

Renal stones result from hereditary or acquired disorders causing supersaturation of stone precursors, deficiency of stone inhibitors, and possibly excess promoters. Supersaturation causes crystallization with mineral precursors, such as calcium and oxalate. Calcium oxalate crystals bind to anionic sialic acid–containing glycoproteins on the apical surfaces of renal tubular epithelial cells, allowing further growth. Other factors that increase stone formation include urinary stasis (medullary sponge kidney), decreased flow (obstruction), increased urine ammonium (infection), dehydration (concentrated urine), and increased urinary alkalinity (renal tubular acidosis [RTA]). Type I RTA promotes stone formation by increasing the release of calcium and phosphorus from bones to buffer chronic acidemia, leading to high levels of calcium and phosphorus in the urine. The acidemia also increases citrate reabsorption in the proximal tubule, resulting in low citrate levels in the urine. The alkaline urine in RTA promotes the formation of calcium phosphate stones. If acidemia is present along with a positive urine anion gap (UNa + UK – UCl), it suggests the presence of RTA.

9. What are the chemical precursors of renal stones?

Relatively high concentrations of salt and acid solutes determine crystalluria and stone formation. Calcium oxalate is most common and is supersaturated to four to five times its solubility in normal urine. Other precursors are calcium phosphate (hydroxyapatite) and calcium phosphate monohydrate (brushite). Uric acid, cystine, struvite (magnesium ammonium phosphate), and mucoprotein are undersaturated stone precursors. Drugs, such as ascorbic acid (conversion to oxalate) and triamterene (nidus for stone formation), also may promote renal stone formation.

10. What are the main inhibitors of renal stone formation, and how do they work?

Several inhibitors work in concert to prevent the formation and growth of kidney stones. Citrate binds to calcium, reducing its availability to form calcium oxalate crystals. It also increases the solubility of calcium oxalate crystals, further impeding their growth and aggregation. Similarly, pyrophosphate and magnesium hinder the nucleation, growth, and aggregation of calcium phosphate and calcium oxalate crystals. Nephrocalcin also specifically targets calcium oxalate crystal growth and aggregation.

Uromodulin (Tamm-Horsfall protein), uropontin, and glycosaminoglycans inhibit the growth and aggregation of calcium oxalate crystals and prevent these crystals from adhering to the renal tubular cells, thus reducing the risk of stone formation. Uromodulin also binds calcium and limits its availability for crystal formation. Generally, inhibitors impair the transformation of stone precursors into a focus for crystallization, nucleation, and stone growth and provide a multipronged defense against developing kidney stones.

11. What is nephrocalcin, and what role does it play in forming renal stones?

Nephrocalcin is an anionic protein produced in the proximal renal tubule and Henle's loop. Its primary role is to inhibit the formation of kidney stones by preventing crystal nucleation, growth, and aggregation. However, researchers have found structurally and functionally defective nephrocalcin in the matrix of many calcium stones, suggesting that while normal nephrocalcin inhibits stone formation, abnormal nephrocalcin may promote it by binding calcium and forming a nidus for crystallization.

12. What are the promoters of renal stone formation?

Promoters of renal stone formation are poorly characterized but are believed to be primarily urinary mucoproteins and glycosaminoglycans. Under certain conditions, promoters enhance the formation of renal stones.

13. How does the kidney handle calcium, and what is the role of medications?

The kidney maintains calcium balance by filtering and reabsorbing a substantial portion of serum calcium. The glomerulus filters 60% of serum calcium, which includes free-ionized calcium (50%) and complexed calcium (10%). The renal tubules then reabsorb approximately 98% of this filtered calcium. This reabsorption occurs in different segments: 60% in the proximal convoluted tubule, 30% in Henle's loop, and 10% in the distal tubule. Certain medications can modify this reabsorption process. For instance, loop diuretics like furosemide inhibit calcium reabsorption in Henle's loop, increasing urinary calcium excretion.

In contrast, thiazide diuretics enhance calcium reabsorption in the distal tubule by blocking the sodium-chloride cotransporter (NCC). This action indirectly stimulates epithelial sodium channels (ENaC) as sodium and water move through the distal nephron, triggering the renin-angiotensin-aldosterone system (RAAS) and aldosterone. The elevated aldosterone further stimulates ENaC and Na+/K-ATPase activity, resulting in sodium, potassium, and water loss but increased calcium reabsorption.

Amiloride, a potassium-sparing diuretic, inhibits ENaC in the distal convoluted tubule and collecting duct, which decreases sodium reabsorption. This action creates a more positive luminal charge, reducing the electrochemical gradient for potassium secretion and thus decreasing potassium excretion. The inhibition of ENaC leads to changes in cellular and luminal electrochemical gradients in the proximal convoluted tubule (PCT), enhancing sodium and calcium reabsorption primarily in the PCT and, to a lesser extent, calcium reabsorption in the distal convoluted tubule (DCT). This results in reduced urinary calcium excretion. Therefore amiloride can be used with thiazide diuretics to treat kidney stones by lowering urinary calcium and mitigating the hypokalemia induced by thiazides.

Additionally, parathyroid hormone (PTH) enhances calcium channel activity in the distal tubule, further promoting calcium reabsorption in this segment.

14. How would you calculate the normal filtered and excreted load of urinary calcium?

The serum calcium concentration is normally about 10 mg/dL. The kidney filters complexed and free calcium, which comprise 60% of the total, or 6 mg/dL. The normal glomerular filtration rate (GFR) is 120 mL/min. Thus, the filtered calcium load is 6 mg/100 mL × 120 mL/min × 1440 min/day = 10,368 mg/day. Because the kidney reabsorbs 98% of the filtered calcium, only 2% is excreted. Thus, the kidney normally excretes about 200 mg of calcium/day (10,368 mg/day × 0.02 = 207 mg/day). If the excreted calcium level increases to 5%, the urinary calcium level increases to 500 mg/day.

15. How do the serum calcium level and dietary sodium intake affect hypercalciuria?

The kidney is the first defense against hypercalcemia; most nonrenal causes of hypercalcemia cause an increase in filtered calcium and urinary calcium excretion. Increased sodium delivery to Henle's loop and the distal tubule also raises urinary calcium. Each 100 mEq of sodium excretion raises urinary calcium excretion by 40 mg in nonstone formers. In hypercalciuric stone patients, calcium excretion increases to 80 mg per 100 mEq sodium excretion. Higher dietary sodium intake increases urinary sodium excretion; thus, restricting dietary sodium reduces urinary calcium excretion. In patients with kidney stones, the recommended daily dietary sodium intake is <100 mEq (2300 mg) or about one teaspoon of salt (6000 mg).

16. What is the etiology and pathophysiology of idiopathic hypercalciuria (IH)?

IH affects 10% of the general population and 40% of stone formers. The four types of IH are absorptive hypercalciuria (AH)-I, AH-II, AH-III, and resorptive hypercalciuria (RH). AH-I and AH-II result from increased intestinal sensitivity to calcitriol with intestinal calcium hyperabsorption plus higher numbers of vitamin D receptors in osteoblasts, causing greater bone resorption and resorptive hypercalciuria. The latter accounts for decreased bone mass seen in many patients with AH-I and in some of those with AH-II. AH-III, an unusual disorder, is caused by a renal phosphate leak with urinary loss of phosphate, decreased serum phosphate, and increases in renal calcitriol production and intestinal calcium absorption. The phosphaturic factor, fibroblast growth factor 23 (FGF23), is increased in some patients with calcium nephrolithiasis, hypophosphatemia, and renal phosphate leak. RH is characterized by impaired renal tubular reabsorption of calcium, which causes a decrease in serum calcium, elevations in PTH and calcitriol, and increases in bone resorption and intestinal calcium absorption.

17. How would you distinguish among the various forms of IH?

See Table 22.1.

18. When is it necessary to distinguish among the various forms of IH?

Only complicated nephrolithiasis unresponsive to usual therapy requires differentiation (see the list of Websites at the end of the chapter).

19. What explains the differences in phosphorus and PTH serum levels in AH-III and RH?

Serum phosphorus is low in AH-III because of a renal phosphate leak. The level of intact PTH is high in RH because the primary defect is decreased renal tubular calcium reabsorption, causing relative hypocalcemia that stimulates PTH.

TABLE 22.1 Forms of Idiopathic Hypercalciuria

LABORATORY VALUE	AH-I	AH-II	AH-III	RH
Serum calcium	Normal	Normal	Normal	Normal
Serum phosphorus	Normal	Normal	↓	Normal
Serum intact PTH	Normal	Normal	Normal	↑
24-hour urinary calcium (1-g calcium diet)	↑	↑	↑	↑
Urine Ca/Cr ratio (1-g calcium load)	↑	↑	↑	↑
24-hour urinary calcium (400-mg calcium diet)	↑	Normal	↑	↑
Fasting urinary calcium (mg/dL GFR)	Normal	Normal	↑	↑

↑, Increased; ↓, decreased; *AH*, absorptive hypercalciuria; *Ca/Cr*, calcium/creatinine; *GFR*, glomerular filtration rate; *IH*, idiopathic hypercalciuria; *PTH*, parathyroid hormone; *RH*, renal hypercalciuria. See questions 17–20.

20. How do changes in calcium intake help distinguish the different types of absorptive hypercalciuria and renal leak hypercalciuria? (See Table 22.1.)

In AH-II, the 24-hour urine calcium normalizes with a restricted calcium diet (400 mg/day) because the absorptive excess is not as severe. However, the 24-hour urine calcium during calcium restriction remains high in AH-I because of marked calcium hyperabsorption. The 24-hour urine calcium also remains high in AH-III because hypophosphatemia decreases renal tubular calcium reabsorption, and in RH because impaired renal tubular calcium reabsorption is the primary defect.

High 24-hour urinary calcium is >4 mg/kg ideal body weight. Normal 24-hour urinary calcium with a 400-mg/day calcium restriction is <200 mg/day. For improved accuracy, urinary calcium excretion is sometimes expressed as milligrams of calcium per 100 milliliters of GFR to account for changes related to altered kidney function. The normal fasting urine calcium level is <0.11 mg/100 mL GFR. The normal urine Ca/Cr ratio is <0.20 after a 1-g oral calcium load.

An example of calculating mg/100 mL GFR is as follows: given a 24-hour urine excretion of 150 mg of calcium and GFR = 100 mL/min. GFR 100 mL/min X 1440 min/day = 144,000 mL/day. 150 mg calcium/day/144,000 mL/day = 0.0010 mg/mL or 0.10 mg/100 mL GFR.

21. What defines low serum phosphorus on an 800-mg/day phosphorus-restricted diet?

Low serum phosphorus is <2.5 mg/dL on an 800-mg/day phosphorus diet.

22. What causes hyperoxaluria?

Approximately 14% of urinary oxalate comes from dietary absorption. The remainder is from metabolism of glyoxylate and ascorbic acid. Autosomal recessive hereditary hyperoxaluria causes increased oxidation of glyoxylate to oxalate. Enteric hyperoxaluria, which is more clinically significant, occurs with small bowel resection, bypass, or inflammation. Bile salt and fat malabsorption can occur in small bowel disease, leading to increased delivery of bile salts and fats to the colon. Bile salts damage the colonic mucosa and increase colonic permeability, allowing for more oxalate absorption. Intestinal fatty acids bind calcium and magnesium, reducing the availability of these minerals to bind intestinal oxalate. Low-calcium diets have the same effect. Excess intestinal oxalate is primarily absorbed in the colon damaged by bile salts. People with small bowel disease and an ileostomy do not hyperabsorb oxalate. Consuming excessive dietary oxalate or ascorbic acid (>2 g/day) also leads to hyperoxaluria. Oxalobacter (O.) formigenes, which metabolizes oxalate in the intestinal tract, plays a role in reducing oxalate absorption. Recent evidence suggests that a healthy intestinal microbiome, including the gram-negative bacteria O. formigenes, is important for reducing gut oxalate absorption and urinary oxalate excretion.

23. Why is hyperoxaluria important in nephrolithiasis?

Oxalate is a major component of the most common kidney stones, including calcium oxalate and calcium oxalate/phosphate stones. High dietary oxalate intake strongly contributes to hyperoxaluria, necessary for the supersaturation needed to form calcium oxalate stones.

24. How does hyperuricosuria contribute to renal stones?

Uric acid stones occur in approximately 25% of people with symptomatic tophaceous gout due to excessive urinary uric acid (>600 mg/day). This supersaturates the urine, leading to crystallization and formation of uric acid stones. Interestingly, most uric acid stone formers do not have gout, hyperuricemia, or hyperuricosuria. Virtually all have a urinary pH <5.5, which promotes uric acid stone formation. Approximately 25% of calcium stone formers have hyperuricosuria. Hyperuricosuria decreases the solubility of calcium oxalate and may increase calcium oxalate stone formation due to the interference of monosodium urate with inhibitors. This disorder, known as hyperuricosuric calcium nephrolithiasis, is characterized by normal serum calcium, urinary uric acid >600 mg/day, urine pH >5.5, and recurrent calcium stones.

25. How does urinary pH relate to renal stones?

Because uric acid has a pKa of 5.5, acid urine shifts the equilibrium so that the urinary uric acid concentration is higher than that of sodium urate. At urine pH 6.5, only 10% is uric acid, and about 90% is sodium urate. Because uric acid is 100 times less soluble than sodium urate, uric acid stones are more likely to form in acid urine. This equilibrium is so important that uric acid stones virtually never develop unless the urinary pH is <5.5. Because of low urinary pH, uric acid stones occur more frequently in obesity and diabetes. Obesity and type 2 diabetes are associated with insulin resistance, renal steatosis, and renal lipotoxicity. This results in decreased insulin-dependent renal production of ammonia, decreased urinary ammonium excretion, a lower urinary pH, and a propensity for uric acid stones. Additionally, obesity and type 2 diabetes are associated with hyperinsulinemia, which decreases distal nephron calcium reabsorption and increases net calcium excretion and the risk for calcium stones. Cystine stones are also more likely in acid urine, whereas calcium phosphate (brushite) stones usually form primarily in alkaline urine (pH >7.0). Calcium oxalate stones may develop in either acid or alkaline urine.

26. What conditions cause low levels of urinary citrate?

Patients with hypocitraturia excrete <320 mg/day, while optimal levels are closer to 640 mg/day. Idiopathic (primary) hypocitraturia occurs in <5% of patients with calcium stones; secondary hypocitraturia may occur in 30%. The glomerulus freely filters citrate; the proximal renal tubule reabsorbs 75% and little citrate is secreted; therefore about 25% of filtered citrate is excreted in the urine. Most causes of secondary hypocitraturia decrease urinary citrate by increasing proximal renal tubular reabsorption. Secondary causes of low urinary citrate include dehydration, high animal protein consumption, low fruit and vegetable intake, metabolic acidosis, hypokalemia, thiazide diuretics, carbonic anhydrase inhibitors, magnesium depletion, renal tubular acidosis, and diarrhea. Diarrhea also causes direct gastrointestinal loss of citrate and magnesium.

27. What is the role of diet in forming kidney stones?

The high animal protein (beef, poultry, pork, fish) intake of many Americans (>1.5–2 g/kg/day) acidifies the urine with phosphoric, sulfuric, and uric acids. Mild acidemia from protein metabolism increases calcium release from bone, increases filtered calcium, decreases calcium reabsorption, increases urinary calcium, increases citrate reabsorption, decreases urinary citrate, and raises the risk for nephrolithiasis. Ketogenic, higher-protein diets, such as the Atkins diet, worsen these effects. Increased sulfates and uric acid may act as cofactors in forming calcium oxalate and uric acid stones. High sodium intake increases urinary calcium excretion (see question 15). High calcium intake (>1500 mg) also contributes to hypercalciuria. However, low calcium intake (<600 mg) without low oxalate intake decreases oxalate binding in the gut, increasing oxalate absorption and urinary oxalate. A diet high in protein and salt (sodium chloride [NaCl]) impairs citrate excretion by inducing subclinical intracellular and extracellular acidosis and increased citrate reabsorption. Fructose adversely affects the microbiome, increases uric acid production, and increases the risk of nephrolithiasis. Diets high in calories and low in fiber, fruits, and vegetables are associated with obesity and increased nephrolithiasis. High dietary oxalate increases calcium oxalate crystalluria and nephrolithiasis. Typical diets contain about 200–300 mg of oxalate, but to decrease calcium oxalate stones, oxalate intake must be reduced to 50–100 mg daily. See Table 22.2 on the oxalate content of foods and the websites on how to eat a low-oxalate diet at the end of this chapter. The way a food is cooked can also change its oxalate content. Orange juice may help prevent kidney stones by increasing urinary potassium and citrate. Potassium citrate

TABLE 22.2 Oxalate Content of Selected Foods*

High-Oxalate Foods (>100 mg/serving)

- Vegetables: Spinach, Beet Greens, Rhubarb, Beets
- Fruits: Starfruit
- Legumes: Navy beans, Baked beans, Tofu
- Nuts & Seeds: Sesame seeds
- Grains: Buckwheat, Wheat bran, Rice bran, Corn bran
- Miscellaneous: Cocoa powder, Chocolate, Tea (especially black tea), Ovaltine

Moderate-Oxalate Foods (10–100 mg/serving)

- Vegetables: Mushrooms, Okra, Sweet Potatoes, Leeks, Celery, Collard Greens, Mustard Greens
- Fruits: Blackberries, Dried Figs, Raspberries, Kiwi, Tangerines, Concord Grapes, Gooseberries, Citrus Peel, Blueberries, Strawberries
- Legumes: Chickpeas, Kidney beans
- Nuts & Seeds: Almonds, Cashews, Peanuts, Sunflower seeds, Wheat germ
- Grains: Quinoa, Millet
- Beverages: Roasted coffee

Low-Oxalate Foods (<10 mg/serving)

- Vegetables: Cucumbers, Summer Squash, Cabbage, Cauliflower, Broccoli, Asparagus, Onions, Turnip Greens
- Fruits: Most fruits (apples, bananas, citrus fruits (flesh), grapes (most varieties), melons, peaches, pears, plums), Pineapple, Mango, Watermelon, Grapefruit, Lime, Corn
- Legumes: Most beans (except navy beans, chickpeas, kidney beans), Lentils, Peas
- Nuts & Seeds: Most other nuts and seeds (e.g., walnuts, pecans, pumpkin seeds)
- Grains: Most grains (e.g., rice, oats, barley, corn)

*To effectively reduce the risk of kidney stones, it is essential to make informed dietary choices, to be aware of the oxalate content in various foods, and to aim to decrease oxalate intake. For a comprehensive guide on managing oxalate intake, please refer to Table 22.2 and the specific websites and references provided at the end of this chapter. These resources offer valuable information about the best dietary choices and oxalate content.

as Urocit-K is commonly prescribed to increase urinary citrate; if from Micromedex, Urocit-K at 60 mEq/day raises urinary citrate by approximately 400 mg/day and increases urinary pH by approximately 0.7 units. However, an 8-oz glass of orange juice supplies 12 mEq potassium and 38 mEq citrate, which is more than that provided by a 10-mEq/1080-mg tablet of Urocit-K. Cranberry juice has mixed reviews, but data now suggest that it should not be used excessively in stone disease because it may increase urinary oxalate. Lemon and lime citric acid juices supply little potassium and only one-third as much citrate as orange juice. Although potassium citrate juices are more powerful at stone inhibition, nearly all citrus drinks are useful. An exception is grapefruit juice, which increases urinary oxalate and may increase stone formation by 30% to 50%. The clinician should be flexible with the patient's choice of fluid because the importance of fluid intake may outweigh some of the theoretical negatives of the drink.

28. What are the presenting symptoms and signs of renal stones?

While approximately 30% of renal stones are asymptomatic and incidentally found on radiographic studies, the majority (70%) present with symptoms, the classic being excruciating unilateral flank pain that waxes and wanes, often accompanied by hematuria. The pain typically starts in the posterior lumbar area and radiates anteroinferiorly. Other symptoms may include nausea, vomiting, sweating, fever, and chills. Patients with renal colic often appear acutely ill and restless. Physical examination may reveal tenderness and guarding of the lumbar area, with discomfort worsening on deep abdominal palpation. Rebound tenderness is typically absent. A urinary tract infection may be present, and any obstruction is usually unilateral. Clinical evidence of renal failure is typically absent. It is important to note that kidney stone pain can mimic other medical conditions that may suggest the location of the stone, such as acute cholecystitis (right ureteropelvic junction), acute appendicitis (lower right ureter), acute diverticulitis (lower left ureter), acute cystitis (ureterovesical junction), and acute pyelonephritis (proximal obstructing stone).

29. What is important in the kidney-stone patient's history and physical examination?

Key aspects to consider in a kidney-stone patient's history include fluid intake, sources of excess calcium, salt, oxalate, uric acid, and protein, as well as present, past, and family histories of stone disease. A review of all medications, with a focus on those associated with stone formation (e.g., guaifenesin, ephedrine, indinavir, triamterene, sulfonamides, acyclovir, and vitamins A, C, and D), is also crucial. The physical examination is typically most informative during acute episodes, where it is important to assess for signs of complications such as infection or obstruction (see question 28).

30. What tests are appropriate in the diagnosis and management of kidney stones?

Perform a complete urinalysis and focus on pH, hematuria, pyuria, bacteriuria, and crystalluria. If the pH is high or there is bacteriuria, order a urine culture. Perform appropriate radiographic studies (see question 34). Have the patient strain all urine and save the stone, if passed, for stone analysis. If this is the patient's first stone, the pain subsides, and the stone is <5 mm in diameter, conservative management with follow-up for several months is acceptable. Greater than 50% of stones in the proximal ureter and 75% in the distal ureter <5 mm diameter pass spontaneously. Order vitamin D and a blood chemistry panel that includes serum sodium, potassium, chloride, carbon dioxide, creatinine, calcium, albumin, phosphorus, magnesium, and uric acid. Consider serum PTH measurements and a random urine to determine the Ca/Cr ratio. The patient will need a 24-hour urine test for creatinine, sodium, calcium, phosphorus, magnesium, oxalate, citrate, uric acid, and urinary supersaturation. A 24-hour urine collection is considered adequate if the creatinine excretion falls within the normal range for the patient's weight and gender (creatinine/weight [kg] ratio of 10 to 20 mg/kg in women and 15 to 25 mg/kg in men). Repeat 24-hour urine testing may be helpful to assess the response to treatment after 6 weeks. Consider specialized 24-hour urine testing with laboratories such as LabCorp's Litholink or ARUP's stone-forming risk panel for in-depth analysis of stone-forming risk factors. These panels provide detailed evaluation, including supersaturation assessment, and can aid in monitoring therapy. Patients should discontinue multivitamins 5 days before collection to avoid interference from antioxidants. If the patient experiences persistent symptoms, has a stone larger than 5 mm, or shows evidence of obstruction, consult a urologist for further evaluation and management.

31. What is the management for patients with symptomatic and asymptomatic kidney stones?

Kidney stones rarely require procedural intervention unless they cause or are likely to cause pain, obstruction, infection, or significant bleeding. Ureteral stones may also be treated conservatively (monitored) if there is no renal failure, fever, obstruction, infection, or pain. Pain can be controlled with nonsteroidal antiinflammatory drugs, but opioids may be needed for acute pain exacerbations. Stones <5 mm diameter have a 75% chance of passing spontaneously within 4–6 weeks, while those >10 mm usually do not. Passage of stones ranging from 5–10 mm diameter is variable. Medical expulsive therapy (MET) with alpha-blockers, such as tamsulosin (0.4 mg daily), the calcium channel blocker nifedipine extended-release (ER) (30 mg daily), and the phosphodiesterase type 5 inhibitor tadalafil (5–10 mg daily), may increase distal ureteral stone passage in 65% of cases by reducing ureteral spasm and improving peristalsis during acute colic episodes. MET therapy usually works within 4 weeks. While tamsulosin monotherapy has proven effective, combination MET therapy with multiple agents appears more successful. Addition of corticosteroids may enhance MET success by reducing ureteral inflammation and spasm. Refer patients with symptomatic stones, stones >5 mm diameter, or multiple stones for urologic evaluation. Unless contraindicated, preventing stone recurrence requires:

- Fluid intake: 2–3 L/day to increase urine output to >2 L/day.
- Sodium intake: <2 g/day.
- Protein intake: 0.8–1.0 g/kg ideal body weight with more plant protein (2/3 of the total) and less animal protein (1/3).
- Calcium intake: 1000–1200 mg/day
- Avoidance: grapefruit juice, excessive calcium supplements, high-oxalate foods, and vitamin C.

Adequate calcium intake (1000–1200 mg/day) is essential for bone health and kidney stone prevention. If the diet does not provide enough calcium, calcium citrate (not calcium carbonate) supplements should be taken twice daily with meals to achieve a total calcium intake (from meals and supplements) of 1000–1200 mg/day. Measurement of 24-hour urine calcium, both with and without the calcium supplements, should be done to assess if the supplement leads to excessive urinary calcium levels that may necessitate adjustments. During ureteral surgery for symptomatic stones, removing small, asymptomatic stones in either kidney has been shown to reduce the risk of relapse. This approach does not appear to increase complications and should be discussed with the urologist performing the procedure (question 39).

32. What is the clinical significance of the urinalysis in patients with renal stones?

Urinalysis in patients with renal stones often reveals macroscopic or microscopic hematuria. Crystalluria may also be present, but its absence does not rule out stones. Crystals can sometimes suggest the type of stone. However, crystals can also form in cooled specimens of normal urine and are thus not always clinically significant. An exception is cystine crystals, which are indicative of cystinuria.

Urine pH can provide clues about the type of stone:

- Acidic urine (pH <5.5) suggests uric acid or cystine stones.
- Neutral urine (pH 6.0–6.5) is often associated with calcium oxalate stones.
- Alkaline urine (pH >6.5–7.0) suggests calcium phosphate stones.
- Persistently alkaline urine (pH >7.0–7.5) indicates the presence of urea-splitting organisms (e.g., Proteus, Pseudomonas, Klebsiella), suggesting struvite stones, which require alkaline urine for formation.

33. What are the characteristics of urinary crystals in patients with renal stones?

Understanding urinary crystals helps diagnose the cause of renal stones and guide treatment. It is crucial to examine a fresh and warm urine sample as crystals can form as the urine cools in normal urine, leading to misleading findings. However, cystine crystals always indicate cystinuria, regardless of temperature or freshness of the urine.

The distinct characteristics of various crystal types are as follows:

- **Calcium Oxalate Monohydrate Crystals** may exhibit diverse shapes, including dumbbells, needles, or ovals. Oval-shaped crystals can resemble red blood cells, potentially leading to confusion.
- **Calcium Oxalate Dihydrate Crystals** are pyramid-shaped and envelope-like, reflecting their characteristic octahedral structure.
- **Calcium Phosphate and Uric Acid Crystals** are too small to be visualized clearly under standard light microscopy and often appear as amorphous debris. However, uric acid crystals are characteristically yellow-brown, aiding their identification.
- **Uric Acid Dihydrate Crystals** are less commonly encountered, rhomboid-shaped, or resemble the four-sided diamonds on playing cards.
- **Cystine Crystals** present as flat, hexagonal plates reminiscent of benzene rings. Their presence invariably signifies cystinuria, a disorder characterized by impaired cystine reabsorption in the kidneys.
- **Struvite Crystals (Magnesium Ammonium Phosphate)** are rectangular prisms that resemble coffin lids. Their presence is associated with urinary tract infections caused by urease-producing bacteria.

34. How do radiographic tests help evaluate patients with renal stones?

Radiographic tests are crucial for evaluating patients with renal stones. Clinicians must understand the strengths and limitations of each imaging modality to choose the most suitable tests. These tests help identify the type of stone, monitor its progress, determine the level of obstruction, and assess the kidneys for associated complications. It is important to note that uric acid, xanthine, and indinavir stones cannot be seen on some tests, like Kidney-Ureters-Bladder (KUB). This is an important consideration when selecting the appropriate imaging modality. Here is a breakdown of how different tests contribute.

Kidney–Ureters–Bladder (KUB): A plain abdomen radiograph (KUB) is recommended for all stone formers. It shows stones with specific features:

- Calcium stones appear small, dense, and circumscribed.
- Cystine stones are faint, soft, and waxy.
- Struvite stones are typically irregular and dense.

KUB can also be used to monitor a stone's progress and visualize the size and location of the kidneys. Phleboliths, which can be confused with ureteral stones, show a lucent center on KUB.

Intravenous Pyelography (IVP): IVP helps localize stones within the urinary tract and assess the degree and location of obstruction. A radiolucent filling defect on IVP suggests a uric acid stone.

Ultrasonography: This test reveals the size and location of larger stones and is sensitive for diagnosing obstruction. It is also valuable for evaluating the kidneys for hydronephrosis (swelling due to obstruction) and other abnormalities. Ultrasonography may be the preferred choice when radiation exposure should be minimized, such as in pregnancy.

Non-contrast Helical (Spiral) Computed Tomography (CT): This is the initial radiographic procedure of choice for most cases of suspected stone disease due to its high sensitivity and specificity for detecting stones. It requires no patient preparation and typically employs a renal stone protocol with thin collimation (1–3 mm slices) acquired during a single breath-hold without intravenous contrast.

Dual-Energy CT (DECT): DECT is a newer technique that assesses stone attenuation at two different peak kilovolt (kVp) levels. It can discriminate among several subtypes of urinary calculi, including differentiating between uric acid and calcium oxalate stones, without requiring a formal stone analysis. While not widely available, DECT may eventually replace non-contrast helical CT in some settings.

MRI: While not routinely used, MRI can be helpful in specific situations, such as evaluating pregnant patients or those with contrast allergies.

Nuclear Scintigraphy: This can assess renal function and detect obstruction but is less commonly employed for initial stone evaluation.

Plain Film Tomography: Largely replaced by CT but might be mentioned historically or in resource-limited settings.

Indinavir, Atazanavir, and Darunavir Stones: The increasing use of protease inhibitors in HIV treatment has led to a rise in the prevalence of these stones. If suspicion is raised based on the patient's history, physical examination, and signs of obstruction, contrast-enhanced CT scanning or IVP may be necessary for diagnosis.

35. Which medications are used to treat various stone-forming conditions?

See Table 22.3.

36. What are special considerations in drug therapy for nephrolithiasis prevention?

Most stones are comprised of calcium oxalate and form because of high urinary calcium and low citrate levels. Typically, thiazides are used to lower urinary calcium levels, while citrate is given to increase urinary citrate levels after all dietary recommendations have been followed. Potassium citrate, rather than sodium citrate, is recommended for increasing urine pH to >6.5–7.0 to prevent uric acid and cystine stones. However, that pH is difficult to achieve with potassium citrate alone; supplementing with citrate juices may be needed to provide the 100 mEq of alkali needed to maintain that urine pH. Sodium citrate should be avoided, since it increases urinary sodium and calcium excretion, which may promote calcium stone formation in alkaline urine. Cystine stone formers require higher fluid intake to reduce urinary cystine below its solubility limit of 200–250 mg/L and to produce a urine output of 3 L/day. The cystine-binding thiol drugs, tiopronin and penicillamine, help reduce urinary cystine and form soluble complexes with cystine. Tiopronin has fewer side effects and should be tried first. Dietary purine and fructose restriction, adequate fluid intake, and potassium citrate are often the only therapies necessary for uric acid stones if uricosuria is <800 mg/day. The xanthine oxidase inhibitor, allopurinol, can be used with potassium citrate if uric acid stones continue or hyperuricemia is more severe. Cellulose sodium phosphate (CSP) should be used only for refractory stone disease in AH-I. CSP binds calcium and magnesium in the gut and decreases absorption of both; however, it may worsen osteopenia and increase urinary oxalate. Magnesium should be replaced as required. Bone mass should be monitored and osteopenia treated as necessary.

37. Why are thiazide diuretics the first-line drug therapy for hypercalciuria-induced nephrolithiasis?

Hypercalciuria, or excessive urinary calcium excretion, is a major risk factor for the formation of calcium-based kidney stones. Thiazide diuretics are the first-line therapy for hypercalciuria-induced nephrolithiasis because thiazides reduce urinary calcium excretion by increasing calcium

TABLE 22.3 Oral Drug Therapy for Renal Stones

DISORDER	DRUG	DOSAGE
Absorptive type I	Chlorthalidone* Hydrochlorothiazide Potassium citrate Cellulose sodium phosphate Magnesium gluconate Magnesium oxide	12.5–50 mg 1 x daily 12.5–25 mg 2 x daily 10–30 mEq 3 x daily 5 g 1–3 x/day with meals 1–1.5 g 2 x daily 400 mg 2 x daily
Absorptive type II	Chlorthalidone* Hydrochlorothiazide	12.5–50 mg 1 x daily 12.5–25 mg 2 x daily
Renal phosphate leak	Neutral sodium phosphate	500 mg 3 x daily
RH	Chlorthalidone* Hydrochlorothiazide	12.5–50 mg 1 x daily 12.5–25 mg 2 x daily
Hypocitraturia	Potassium citrate	10–30 mEq 2–3 x daily
Hyperuricosuria	Potassium citrate Allopurinol	10–30 mEq 2–3 x daily 100–300 mg 1 x daily
Enteric hyperoxaluria	Potassium citrate Magnesium gluconate Calcium citrate Calcium carbonate Cholestyramine Pyridoxine	10–30 mEq 3 x daily 1–1.5 g 2 x daily 950 mg 4 x daily 250–500 mg 4 x daily 4 g 3 x daily 100 mg 1 x daily
Cystinuria	Potassium citrate Tiopronin Penicillamine Pyridoxine	10–30 mEq 3 x daily 100 mg 2–4 tabs 3 x daily 250–500 mg 4 x daily 50 mg 1 x daily
Struvite stones	Acetohydroxamic acid	250 mg 1–2 tabs 3 x daily
Medical expulsion therapy (MET)	Tamsulosin Nifedipine ER Tadalafil	0.4 mg 1 x daily 30 mg 1 x daily 10 mg 1 x daily

Note: All medications are taken orally. Dosages represent approximate ranges, not absolute recommendations. Adjust each drug based on the patient's tolerance. Use the lowest dosage needed to achieve the desired effect and avoid side effects. Always combine drug therapy with appropriate dietary changes and fluid intake. Potassium citrate is better tolerated in lower dosages, taken three times daily with meals. However, extended-release potassium citrate can be taken twice daily to improve compliance. Potassium citrate is often needed to correct thiazide-induced hypokalemia and hypocitraturia (see question 36).

*Chlorthalidone (12.5–50 mg daily) or indapamide (1.25–5 mg daily) is preferred to hydrochlorothiazide (12.5–25 mg twice daily) because the once-daily dosing should improve adherence and provide more effective therapy (see question 37). Follow-up 24-hour urine testing is usually indicated to determine treatment effectiveness.

reabsorption primarily in the renal distal tubule and indirectly in the proximal tubule. Dosing and precautions are listed below.

- **Thiazide Diuretics:** Hydrochlorothiazide is commonly used, with a typical starting dose of 12.5–25 mg twice daily. However, it can lead to potassium and citrate depletion, which should be addressed with potassium citrate supplementation. In addition to hypokalemia and hypocitraturia, thiazide therapy can be associated with hyponatremia, hypercalcemia, hyperuricemia, dysglycemia, and dyslipidemia, so patients should be carefully monitored for these potential problems. The dosage may need to be adjusted based on individual patient response and tolerability, and serum potassium should be checked within 2–3 weeks of starting the thiazide diuretic. The half-life of hydrochlorothiazide is about 10 hours, and, therefore, it is usually dosed twice daily to be effective.
- **Thiazide-like Diuretics:** Chlorthalidone (12.5–50.0 mg daily) with a half-life of about 50 hours or indapamide (1.25–5 mg daily) with a half-life of around 20 hours may be preferred because of their once-daily dosing convenience and less likelihood of lipid disturbances with indapamide.
- **Amiloride** (5–10 mg daily) is a potassium-sparing diuretic. It can be helpful when used alongside thiazide-type diuretics because it reduces urinary calcium and prevents thiazide-induced

hypokalemia (see question 13). However, caution should be taken when using amiloride with potassium supplementation to avoid hyperkalemia.
- **Triamterene:** This potassium-sparing diuretic should be avoided as it can contribute to kidney stone formation.

NOSTONE Trial: The 2023 NOSTONE trial did not demonstrate a favorable effect of thiazides on stone prevention compared to placebo. However, the trial had several limitations, including a short duration of 3 years, the administration of only once-daily hydrochlorothiazide (whereas it is usually dosed twice daily for stone treatment), and the lack of control for dietary factors such as sodium, calcium, and oxalate intake, which are important in stone formers and may have contributed to the negative results. Therefore despite the negative findings of the NOSTONE trial, thiazides remain a primary treatment for calcium nephrolithiasis, and further research is warranted. However, given the negative results with once daily hydrochlorothiazide, consider chlorthalidone 12.5–50 mg once daily or hydrochlorothiazide 12.5 to 25 mg twice daily to improve treatment results.

38. How should you treat a symptomatic patient with a renal stone 1 to 2 cm in size?

When treating a symptomatic patient with a 1- to 2-cm kidney stone, it is important to consider the stone size, location, hardness, and composition. These stones are unlikely to pass spontaneously, so all symptomatic patients should be referred to a urologist for further evaluation and management. The best treatment approach will be determined based on a comprehensive assessment of the patient and the stone's characteristics. While surgery may be necessary in some cases (around 10–20% of cases), urologists will typically try less invasive procedures first.

- **Extracorporeal Shock Wave Lithotripsy (ESWL):** Often used for appropriately sized calcium stones in the renal pelvis or proximal ureter.
- **Percutaneous Nephrolithotomy (PCNL) or Mini-PCNL:** Preferred for larger or more complex stones, or when ESWL is contraindicated or unsuccessful, because it offers higher stone-free rates.
- **Ureteroscopy:** Particularly effective for distal ureteral stones >1 cm or when other modalities are unsuitable.
- **Medical Expulsive Therapy (MET):** May be considered an adjunct to facilitate stone passage, especially for smaller stones within this size range (see question 31).

39. How should you treat an asymptomatic patient with a renal stone 1 to 2 cm in size?

Managing asymptomatic renal stones 1 to 2 cm in size requires careful consideration and shared decision-making with the patient. While some stones may be monitored conservatively with measures such as increased fluid intake and periodic imaging (as discussed in question 31), others may warrant intervention to prevent complications or future symptoms. The treatment choice should be individualized based on a thorough assessment of the patient and stone characteristics. Urology consultation is recommended for all patients with asymptomatic stones of this size.

Factors influencing the decision to intervene include:

- Stone size and location: Larger stones or those located in areas prone to obstruction are more likely to require treatment.
- Patient factors: Comorbidities, occupation, and patient preferences should be considered.
- Stone growth or associated complications: Evidence of stone growth, recurrent infections, or silent obstruction may necessitate intervention.

Treatment options for asymptomatic stones that do not pass spontaneously include:

- Observation with metabolic evaluation and preventive measures is appropriate for select patients with small, stable stones and a low risk of complications.
- Extracorporeal Shock Wave Lithotripsy (ESWL): Noninvasive fragmentation of stones, particularly suitable for renal or proximal ureteral stones.
- Ureteroscopy (URS): Endoscopic access to the ureter for stone removal or fragmentation, often preferred for distal ureteral stones or those not amenable to ESWL.
- Percutaneous Nephrolithotomy (PCNL) is a minimally invasive surgical approach for larger or complex stones, offering high stone-free rates.
- Other techniques: Less commonly used options include laser lithotripsy, percutaneous ultrasonic lithotripsy, and robotic-assisted surgery.

40. What treatment should be used for stones larger than 2–3 cm?

For stones larger than 3 cm, lithotripsy alone is usually ineffective because of the difficulty in fragmenting and clearing such large stone burdens. The primary treatment approaches for these stones include:

- Endoscopic techniques: Percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS) are commonly used to access and remove or fragment large stones.
- Robotic-assisted surgery: In some centers, robotic surgery is employed for complex or large-volume renal stones, offering potential benefits in precision and dexterity.
- Open surgery: Open lithotomy is rarely performed and is reserved for exceptional cases where other approaches are not feasible.

The optimal treatment strategy for stones >2 cm depends on several factors, including:

- Patient factors: Overall health status, comorbidities, and preferences play a role in decision-making.
- Stone characteristics: Size, location, and composition can influence treatment choice.
- Physician expertise and available resources: The urologist's experience and the availability of specific technologies at the treating center are also important considerations.
- A combination of techniques outlined in questions 38 and 39 is sometimes necessary.

KEY POINTS

Prevalence and Etiology of Nephrolithiasis

- Kidney stone prevalence has increased in the United States and likely relates to dietary and lifestyle changes associated with increased obesity and metabolic syndrome, alterations in the gut microbiome, increased sodium and animal protein intake, and decreased fiber, fruits, vegetables, water, and dietary calcium intake.
- Approximately 14% of the U.S. population has a lifetime risk for at least one kidney stone.
- Kidney stones form primarily because of increased urinary stone precursors (e.g., calcium and oxalate) causing supersaturation, insufficient stone inhibitors (e.g., citrate), abnormal urine pH, or low urine volume.
- Kidney stones are most commonly calcium-based and result from hypercalciuria caused by excess dietary calcium absorption, resorption of bone calcium, increased sodium-associated calcium excretion, and decreased renal calcium reabsorption.
- Because calcium binds oxalate in the gut, insufficient dietary calcium (low-calcium diet) increases oxalate absorption in patients on normal or high-oxalate diets and increases calcium oxalate stones.

Treatment of Nephrolithiasis

- **Stone Size and Passage:** Stones smaller than 5 mm typically pass spontaneously, with distal ureteral stones having the highest passage rate. Stones between 5 and 10 mm have unpredictable outcomes. For ureteral stones under 10 mm, alpha-1 blockers, calcium channel blockers (Nifedipine), or tadalafil may facilitate passage. Stones larger than 10 mm are unlikely to pass without urologic intervention.
- **Preventing Recurrence:**
  - **Hydration:** Encourage 10–12 eight-ounces of fluid daily, including water and citrate-rich beverages ("Dilution is the solution!").
  - **Diet:**
    - Recommend the DASH or Mediterranean diet, modified for low sodium and oxalate intake, especially for calcium oxalate stone formers.
    - Aim for 1000–1200 mg/day of dietary calcium.
    - Limit protein intake to <1.0 g/kg/day, prioritizing plant-based sources over animal protein.
    - Restrict sodium intake to <2000 mg/day.
    - Avoid grapefruit juice and excessive cranberry juice.
    - Limit dietary oxalate, particularly for calcium oxalate stone formers.
    - Reduce ascorbic acid (vitamin C) intake to around 100 mg/day for calcium oxalate stone formers.
  - **Supplements:** Use calcium citrate supplements (not calcium carbonate) with meals only if dietary calcium intake is inadequate.
- **Medication Alternatives:** Potassium citrate for urinary alkalization and citrate replacement, but it can be costly and cause intolerance. Citrus drinks such as orange, lemon, and lime juice can substitute; orange juice is best.
- **Referral for Intervention:** Refer to an urologist if the patient experiences persistent pain, obstruction, infection, severe bleeding, fever, or renal dysfunction.

WEBSITES

1. EMedicine: Nephrolithiasis: http://www.emedicine.com/med/topic1600.htm.
2. EMedicine: Hypercalciuria review: http://www.emedicine.com/med/topic1069.htm.
3. EMedicine: Hyperuricemia and gout review: http://www.emedicine.com/med/topic3028.htm.
4. EMedicine: Hypocitraturia review: http://www.emedicine.com/med/topic3030.htm.
5. EMedicine: Intracorporeal lithotripsy: http://www.emedicine.com/med/topic3034.htm.
6. American Urologic Association: Stone Guidelines—Medical & Surgical. Stone Guidelines - American Urological Association (auanet.org)
7. Favus MJ: Nephrolithiasis: https://www.ncbi.nlm.nih.gov/books/NBK279069/
8. ROKS—Recurrence Of Kidney Stone (2014) | Calculate by QxMD | QxMD
9. Kidney Stone Program—Kidney Stone Program | University of Chicago (uchicago.edu)
10. How To Eat A Low Oxalate Diet | Kidney Stone Program (uchicago.edu)

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CHAPTER 23

Anterior Pituitary Insufficiency (Hypopituitarism)

John J. Orrego

1. What is pituitary insufficiency?

Anterior pituitary insufficiency, also known as *hypopituitarism*, is a syndrome characterized by one or more anterior pituitary hormone deficiencies as a result of aplasia, hypoplasia, compression, infiltration, or destruction of the hypothalamus, pituitary stalk, and/or pituitary gland. Hypopituitarism can be congenital or acquired; familial or sporadic; primary (idiopathic) or secondary; partial or complete; and transient (reversible) or permanent. Posterior pituitary insufficiency, also known as arginine vasopressin deficiency or central diabetes insipidus, characterized by decreased synthesis or release of antidiuretic hormone with ensuing polyuria and polydipsia, is discussed in Chapter 23.

2. Is arginine vasopressin deficiency (central diabetes insipidus) a manifestation of hypopituitarism?

Most adult patients with hypopituitarism do not have coexistent posterior pituitary insufficiency. However, in those in whom arginine vasopressin deficiency is also present, craniopharyngioma, hypophysitis, metastatic cancer, and sarcoidosis should be suspected.

3. How common is hypopituitarism in the general population?

A study conducted in northwestern Spain revealed that the annual incidence of hypopituitarism was 4.2 cases per 100,000 and that the prevalence was 45 cases per 100,000. There were no gender differences in this survey.

4. What causes anterior pituitary insufficiency?

Almost any disease that disturbs the normal interaction between the hypothalamus and the pituitary gland can produce anterior pituitary insufficiency. The most common cause of hypopituitarism is pituitary dysfunction associated with a pituitary adenoma and/or the effect of its treatment (surgery and/or radiation therapy). Among patients with pituitary macroadenomas, one-third will present with one or more pituitary hormone deficiencies. The most common causes of hypopituitarism are shown in Table 23.1.

5. How do patients with pituitary insufficiency initially present?

The clinical manifestations of hypopituitarism are protean and depend on the extent and severity of the specific pituitary hormone deficiencies. If the onset is acute, the patient may be critically ill and present with hypotension and shock, obtundation, and even coma. However, if the onset is chronic and the pituitary deficiency is mild, the patient may only endorse fatigue and malaise.

- *Adrenocorticotropic hormone (ACTH) deficiency (central adrenal insufficiency):* Fatigue, malaise, low-grade fever, diffuse myalgias and arthralgias, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, diarrhea, and postural lightheadedness.
- *Thyroid-stimulating hormone (TSH) deficiency (central hypothyroidism):* Impaired mental activity, weight gain, fatigue, weakness, cold intolerance, dysphonia, somnolence, alopecia, facial puffiness, and constipation.
- *Gonadotropin deficiency (central hypogonadism):* Men report decreased libido, erectile dysfunction, hot flashes, gynecomastia, and infertility. Women complain of oligo/amenorrhea, infertility, decreased libido, hot flashes, vaginal dryness, and dyspareunia.
- *Growth hormone (GH) deficiency:* Fatigue, weakness, increased adiposity, decreased lean mass, exercise intolerance, and impaired sleep quality.
- *Prolactin (PRL) deficiency:* Agalactia or hypogalactia in the postpartum period.

TABLE 23.1 Etiology of Hypopituitarism

Neoplastic: Pituitary adenoma or carcinoma Metastatic disease Hematologic malignancies Craniopharyngioma Parasellar masses (meningioma, germinoma, glioma)
Traumatic: Surgery Radiation Traumatic brain injury
Vascular: Sheehan's syndrome Apoplexy Subarachnoid hemorrhage Aneurysm
Infiltrative/Inflammatory: Hypophysitis Sarcoidosis Histiocytosis X Hemochromatosis
Infectious: Bacterial abscess Tuberculosis Fungal infections Parasitic infections

6. Are there any signs on physical examination that suggest pituitary insufficiency?

Other than delayed relaxation of deep tendon reflexes in patients with overt hypothyroidism (Woltman's sign), there are no specific or pathognomonic findings on physical examination in patients with hypopituitarism.

- *ACTH deficiency:* Postural hypotension, tachycardia, pallor, alopecia, and areolar hypopigmentation. Women with longstanding ACTH deficiency often have loss of pubic and axillary hair.
- *TSH deficiency:* Bradycardia, alopecia, facial/periorbital puffiness, madarosis (loss of the tail of the eyebrows), dysphonia, hypercarotenemia, and delayed relaxation of deep tendon reflexes (Woltman's sign).
- *Gonadotropin deficiency:* If the onset of hypogonadism is prepubertal, both men and women will acquire eunuchoid features, including deficient secondary sex characteristics and excessive growth of the long bones. If the onset is postpubertal, men may have pallor, fine facial wrinkling, scarce body and facial hair, gynecomastia, increased adiposity and decreased muscle mass, and smaller and softer testicles. Women may have alopecia, hirsutism, reduced breast tissue mass, and vaginal atrophy.
- *GH deficiency:* Fine facial wrinkling, increased adiposity, and decreased muscle mass. The onset of GH deficiency before growth plate closure will cause short stature.
- PRL deficiency: Postpartum agalactia.

7. How is hypopituitarism diagnosed?

In the setting of typical and overt manifestations of hypopituitarism, basal serum hormone measurements may suffice. However, in patients with more subtle manifestations, dynamic endocrine testing is usually indicated.

- *ACTH deficiency:* Nonspecific laboratory findings include hyponatremia, normochromic, normocytic anemia, and eosinophilia. In the noncritical setting and if using older polyclonal antibody assays, morning (7–9 AM) serum cortisol levels <3 mcg/dL are highly suggestive of adrenal insufficiency, while those >15 mcg/dL practically rule it out. When cortisol values are between 3 and 15 mcg/dL or if there is any doubt about the diagnosis, standard-dose corticotropin (ACTH) stimulation testing should be performed. An ampule of cosyntropin

(250 mcg) is administered intramuscularly or intravenously, and serum cortisol is obtained at 0, 30, and 60 minutes. Adrenal insufficiency is excluded if either the 30-minute or the 60-minute cortisol level is >18 mcg/dL. When highly specific cortisol assays utilizing LC-MS/MS or a monoclonal antibody are used instead, a cortisol cutoff of 14–15 mcg/dL is more adequate. Baseline cortisol <2 mcg/dL is predictive of subnormal stimulated cortisol levels. It is important for clinicians to be aware of the assay-specific cutoff for the method available in their institution when evaluating patients for adrenal insufficiency. If it is not obvious that the etiology is central in origin, an inappropriately low or normal morning (7–9 AM) plasma ACTH level will confirm this suspicion.

- *TSH deficiency:* Hyponatremia, macrocytic anemia, hyperlipidemia, and elevated creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) can be seen. However, central hypothyroidism is confirmed when the serum free thyroxine (T_4) level is below the laboratory reference range in conjunction with a low or normal, or occasionally a slightly elevated, TSH concentration in the setting of pituitary disease.
- *Gonadotropin deficiency:* Normochromic, normocytic anemia may be seen in men with hypogonadism. Decreased fasting morning (before 10 AM) testosterone levels in men and low estradiol concentrations in premenopausal normoprolactinemic women with oligomenorrhea or amenorrhea, in conjunction with inappropriately low or normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, are indicative of central hypogonadism. In postmenopausal women, the absence of high serum FSH and LH is consistent with gonadotropin deficiency.
- *GH deficiency:* In patients with clear-cut features of GH deficiency, three or more pituitary hormone deficits and an insulin-like growth factor 1 (IGF-1) level below the lower limit of normal for age and gender are indicative of GH deficiency. Otherwise, GH stimulation testing, using appropriately controlled body mass index (BMI) cutoffs to assess peak GH values, is required to make this diagnosis. Because growth hormone–releasing hormone (GHRH) is presently unavailable in the United States and the insulin tolerance test is not commonly performed for fear of complications associated with hypoglycemia, the glucagon stimulation test has become increasingly utilized to rule out GH deficiency. Glucagon 1 mg (1.5 mg if weight >90 kg) is administered intramuscularly and blood for GH and glucose is collected at 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes. A peak GH level <3 µg/L in patients with BMI <30 kg/m^2, and <1 µg/L in those with BMI >30 kg/m^2, is consistent with GH deficiency. In patients with glucose intolerance, the diagnostic accuracy of the glucose stimulation test remains unclear. Recently, the macimorelin stimulation test, with a GH cut-point of 2.8 µg/L, was approved to differentiate patients with normal GH secretion from those with GH deficiency.
- *PRL deficiency:* Low or undetectable serum PRL concentration.

8. What is the role of pituitary magnetic resonance imaging (MRI) scanning in hypopituitarism?

Any patient with unexplained hypopituitarism or hyperprolactinemia, or with symptoms of tumor mass effect, should undergo pituitary MRI scanning with and without contrast. Patients with suspected functional hypopituitarism (i.e., after use/abuse of anabolic–androgenic steroids or glucocorticoids) do not usually need pituitary imaging. Men with unexplained and isolated central hypogonadism with confirmed serum testosterone levels <150 ng/mL should be imaged.

9. How soon after radiation therapy can pituitary insufficiency be expected?

Any radiation fields that include the hypothalamic–pituitary area can cause neuroendocrine dysfunction. Irradiation for sellar and parasellar tumors, primary brain tumors, nasopharyngeal carcinoma, acute lymphoid leukemia, and tumors of the skull base have been shown to compromise hypothalamic/pituitary function. Depending on the radiation dose and the presence of preexisting pituitary disease, it may take from several months to many years for pituitary insufficiency to develop. The 5-year cumulative incidence of GH, LH/FSH, ACTH, and TSH deficiency in patients treated with radiation therapy for pituitary tumors (radiation dose: 30–50 Gy) has been reported as 100%, 63%, 57%, and 31%, respectively, and in those treated with radiation for nasopharyngeal carcinoma (radiation dose: >60 Gy) reported as 61%, 27%, 27%, and 15%, respectively. Regular testing is mandatory to ensure timely diagnosis and early treatment.

10. How common is pituitary insufficiency after traumatic brain injury (TBI)?

The overall incidence of TBI in the United States has been estimated to be 538 cases per 100,000. The likelihood of pituitary insufficiency is directly related to the severity of the injury. Anterior pituitary deficiencies are more common in the acute setting than 3 and 12 months later. In a study of patients with TBI, 76% had hormonal deficiencies in the acute phase; these persisted in only 13% and 11% of the patients after 3 and 12 months, respectively. GH and gonadotropin deficiencies are the two most common disturbances. The causative mechanism seems to be hemorrhagic infarction of the hypothalamus and/or the pituitary gland because of direct damage to these structures, increased intracranial pressure, hypoxia, or bleeding.

11. Describe the different types of hypophysitis.

Hypophysitis is a general term used to describe chronic inflammation of the pituitary gland and can be classified according to the anatomic location of the pituitary involvement, the cause, and the histopathologic appearance. Based on clinical, radiologic, and pathologic findings, the condition is classified as adenohypophysitis, infundibuloneurohypophysitis, and panhypophysitis. Depending on the etiology, it can be considered primary or secondary, the latter having a clear cause. Histopathologically, hypophysitis is classified as lymphocytic, granulomatous, plasmacytic (immunoglobulin G4 [IgG4]–associated), and xanthomatous. Lymphocytic hypophysitis, the most common form, is characterized by a marked infiltration of lymphocytes that populate the pituitary gland both diffusely and occasionally in focal clusters. The lymphocytes are accompanied by scattered plasma cells, eosinophils, and fibroblasts, and by fibrosis in later stages. It is three times more common in women than in men and uniquely presents in association with late pregnancy and the early postpartum period in about 40% of affected women. Hypophysitis may also occur as a complication of immunotherapy for cancer or, more rarely, as part of the antipituitary-specific transcription factor 1 (PIT-1) antibody syndrome, characterized by GH, PRL, and TSH deficiencies in patients with thymoma associated with autoimmunity to PIT-1.

12. What is immune checkpoint inhibitor-associated hypophysitis?

Immune checkpoint inhibitors (ICI) are a novel class of anticancer therapy that encompasses different immunomodulatory antibodies that enhance the immune system. They are currently used in at least 19 different types of cancer and can produce durable or even curative responses in many cases. ICI, by removing key regulators that inhibit T-cell function, not only generate antitumor immunity but may also trigger autoimmune-like reactions in organs not affected by the malignancy called immune-related adverse events. There are four different classes of ICI, and they block cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death-1 (PD-1) and its ligand (PD-L1), or antilymphocyte activating-3 (Lag-3). Ipilimumab, an anti-CTLA-4 agent used for metastatic melanoma, can cause hypophysitis in 2–17% of these individuals. Hypophysitis due to other ICI is relatively uncommon. The median time for the onset of hypophysitis is 12 weeks after starting ipilimumab, and patients usually present with symptoms of tumor mass-effect on the pituitary gland or of those associated with pituitary insufficiency, mainly ACTH and TSH deficiency. Patients with hypophysitis presenting with headaches and/or visual changes could benefit from high-dose glucocorticoids such as 1 mg/kg/day of prednisone, tapered over a couple of weeks. Permanent discontinuation of ICI is not required. Pituitary replacement therapy is usually lifelong.

13. What is pituitary apoplexy?

Pituitary apoplexy is the abrupt damage of most of the anterior pituitary cells, resulting from an infarction of and/or acute hemorrhage into the pituitary gland or a pituitary adenoma. Pituitary apoplexy is the first manifestation of a pituitary macroadenoma in 4–10% of these patients. Precipitating factors include anticoagulation therapy, bleeding disorders, head trauma, diabetes mellitus, and radiation therapy. Patients usually present with severe headaches, obtundation, ophthalmoplegia, visual loss, hypotension, and shock. Acute hemorrhage into a pituitary adenoma on pituitary MRI scanning and demonstration of biochemical hypopituitarism confirm the diagnosis. Rapid glucocorticoid and thyroid replacement therapies and surgical decompression, if needed, are life-saving measures. Of note, small hemorrhages within pituitary adenomas may be incidentally detected during annual MRI these surveillance of these tumors, indicating that small hemorrhagic infactions may go unnoticed.

14. What is empty sella syndrome?

Empty sella turcica occurs as a result of intrasellar herniation of the suprasellar subarachnoid space with compression of the pituitary gland producing, in many cases, a remodeling of the sella; this results from a combination of an incomplete diaphragma sella and increased cerebrospinal fluid pressure. It is classified as primary or secondary. Primary empty sella is more common in obese multiparous women with hypertension. Twenty-nine percent of patients with incidentally discovered primary empty sella and 40% of those presenting with clinical manifestations have hypopituitarism, with hypogonadism being the most frequent impairment. Hypopituitarism is associated with male sex, suspected endocrine disorder, and traumatic brain injury but not with age, BMI, number of pregnancies, or neuroradiological grade. Secondary empty sella is caused by pituitary disease, surgery, or irradiation. The predominant clinical finding in these patients is visual abnormality, resulting from arachnoidal adhesions and traction on the optic apparatus. Some patients can also have mild hyperprolactinemia caused by stretching of the pituitary stalk.

15. What is Sheehan's syndrome?

Sheehan's syndrome is a form of hypopituitarism that occurs in women after delivering a baby because of infarction within the adenohypophysis caused by massive uterine hemorrhage and hypovolemia. Typically, these women are unable to lactate their newborn and have persistent amenorrhea and symptoms of hypocortisolemia and hypothyroidism. Pituitary MRI imaging shows an atrophic or small pituitary gland and, sometimes, an empty sella. Pathologic studies have shown replacement of organizing necrotic areas by a fibrous scar. The pituitary gland cannot regenerate; new cells do not form to replace the necrotized cells. With modernization of medicine and improved obstetric care, the incidence of Sheehan's syndrome has plummeted in industrialized countries.

16. Describe functional causes of pituitary insufficiency.

It is important to exclude functional hypopituitarism when patients present with an isolated pituitary deficit. Patients receiving high doses of oral glucocorticoids for >6 weeks, or potent inhaled glucocorticoids chronically, or those having frequent articular or epidural glucocorticoid injections have suppressed plasma ACTH levels and may develop transient adrenal atrophy. Depending on dosing and length of exposure to glucocorticoids, these patients may or may not exhibit cushingoid features.

Body builders withdrawing from anabolic–androgenic steroids can exhibit undetectable LH and FSH and very low testosterone levels in conjunction with polycythemia. Hypothalamic amenorrhea, characterized by low serum levels of estradiol, LH, and FSH, can be caused by anorexia nervosa, strenuous exercise, and high levels of stress. Hyperprolactinemia also suppresses secretion of LH, FSH, and gonadal steroids; decreased testosterone or estrogen concentrations usually normalize after correcting hyperprolactinemia with dopamine agonists. Critical illness and high-dose opioids may suppress both the hypothalamic–pituitary–adrenal and the hypothalamic–pituitary–gonadal axes.

17. How is pituitary insufficiency treated?

The goal of therapy is to replace hormone deficits as close to the physiologic pattern as possible.

- *ACTH deficiency:* Hydrocortisone 15 to 20 mg per day, in two or three divided doses, or prednisone 5 mg per day, is commonly used to replace cortisol. Patients using divided doses of hydrocortisone should take 10 to 15 mg in the morning upon awakening and 5 to 10 mg in the afternoon (two-dose regimen), or 10 to 15 mg in the morning and 5 to 10 mg at lunch and again in the late afternoon (three-dose regimen). Because ACTH is not the main regulator of aldosterone secretion, patients with central adrenal insufficiency do not require fludrocortisone. On the other hand, female patients with significant symptoms of depression or anxiety, decreased libido, low energy, or impaired sense of well-being despite optimized glucocorticoid therapy may benefit from a therapeutic trial with dehydroepiandrosterone (DHEA), 25–50 mg per day, for 6 months. If no benefit is perceived by the patient despite morning mid-normal levels of DHEAS, this therapy should be discontinued. Patients should be educated about stress dosing and emergency glucocorticoid administration and instructed about obtaining medical identification jewelry indicating on their emblem the need for urgent parenteral hydrocortisone in the event of an adrenal crisis.

- *TSH deficiency:* Levothyroxine (LT_4) in doses sufficient to achieve and maintain serum free T_4 levels in the mid- to upper half of the reference range should be used to treat central hypothyroidism. Treatment with liothyronine (LT_3) or desiccated thyroid extracts should be discouraged.
- *Gonadotropin deficiency:*
  - If no contraindications are present, men should be treated with testosterone to alleviate hypogonadal symptoms, improve bone mineral density (BMD), and prevent anemia related to testosterone deficiency. The choice of testosterone formulations depends on patient preference, cost, and risk of specific adverse effects.
  - If no contraindications are present, premenopausal women should be treated with hormone replacement therapy until age 45 to 55 years to alleviate vasomotor symptoms of hypoestrogenism, improve vaginal atrophy and dysuria, prevent bone loss, and reduce the risk of cardiovascular disease and mortality. Unopposed estrogens are given to women who have undergone a hysterectomy and combined estrogen–progesterone preparations are used for those with an intact uterus to prevent endometrial hyperplasia.
- *GH deficiency:* GH replacement therapy may be offered to adult patients with rigorously proven GH deficiency, no contraindications, and persistently reduced sense of well-being, energy, quality of life, muscle strength, and lean body mass, despite adequate replacement of other pituitary deficiencies. The starting dose for patients age <60 years is 0.2 to 0.4 mg/day and that for patients age >60 years is 0.1 to 0.2 mg/day. GH replacement results in improved body composition, BMD, muscle strength, and lipoprotein metabolism. Side effects associated with GH replacement include fluid retention, arthralgias and myalgias, carpal tunnel syndrome, paresthesias, and sleep apnea.

18. How are the different hormonal treatments monitored?

Monitoring central adrenal insufficiency and central hypothyroidism is not as clear-cut as monitoring their primary counterparts.

- *ACTH deficiency:* Because there is no reliable marker to determine exact glucocorticoid requirements, dose adjustments depend on clinical status, comorbid conditions, serum electrolyte levels, and the patient's sense of well-being.
- *TSH deficiency:* Serum TSH levels cannot be used to adjust thyroid replacement dosing in patients with central hypothyroidism. Serum free T_4, obtained before the LT_4 dose, should be used instead. The target free T_4 level should be in the mid- to upper half of the reference range.
- *Gonadotropin deficiency:*
  - Testosterone replacement therapy is monitored with serum testosterone levels. In patients on testosterone injections, the testosterone level should be obtained half-way between shots. In those on topical testosterone, it should be obtained 4 to 12 hours after its application. Hematocrit and hemoglobin should be obtained twice a year or sooner as needed to rule out polycythemia.
  - In women on estrogen/progesterone replacement, follow-up includes assessing symptoms and monitoring for side effects. Measuring serum estradiol is not beneficial.
- *GH deficiency:* GH doses should be titrated by 0.1 to 0.2 mg/day at 6-week intervals, targeting age-adjusted IGF-1 levels in the mid normal range. Once this target is achieved, IGF-1 should be measured every 6 months. If side effects occur, the dose should be reduced. Younger patients, those who are morbidly obese, and women, mainly if taking oral estrogens, usually require higher starting and maintenance doses of GH.

19. What are the risks of hormonal overreplacement in hypopituitarism?

Excessive glucocorticoid doses in patients with central adrenal insufficiency can cause weight gain, metabolic syndrome, increased overall and cardiovascular mortality, bone loss, and, especially in men, increased vertebral fracture risk despite the restoration of gonadal status. Low-dose hydrocortisone replacement may increase bone formation and promote a positive bone-remodeling balance. LT_4 overreplacement in central hypothyroidism increases the risk of atrial fibrillation, increases overall and cardiovascular-specific mortality and morbidity, and promotes bone turnover, resulting in an increased fracture risk, mainly in postmenopausal women. Higher LT_4 doses have been associated with a higher prevalence of vertebral fractures. The overall impact of estrogen and testosterone replacement on cardiovascular disease in patients with central hypogonadism is unclear. Estrogen replacement therapy through age 50 years may reduce the risk of cardiovascular disease and mortality.

20. Management of hypopituitarism in pregnancy.

Because fertility is usually impaired in women with pituitary insufficiency, they rarely have spontaneous pregnancies.

- *ACTH deficiency:* Hydrocortisone, which does not cross the placenta, should be the drug of choice. Higher doses may be required (20–40% more), particularly during the third trimester. Dexamethasone, which is not inactivated in the placenta, should be avoided. Pregnant patients should be closely monitored for clinical manifestations of glucocorticoid under- and overreplacement. Stress dosing is recommended during the active phase of labor.
- *TSH deficiency:* Serum TSH levels cannot be used to adjust thyroid replacement dosing in patients with central hypothyroidism. Serum free T_4, obtained before the LT_4 dose, should be used instead. The target free T_4 level should be in the mid to upper half of the reference range.
- *GH deficiency:* Because there are no prospective studies evaluating the efficacy and safety of GH therapy during pregnancy, and the fact that the placenta synthetizes GH, GH replacement therapy should be discontinued during pregnancy.

21. Do antiepileptic medications interact with hormone replacement therapy?

Some antiepileptic drugs (AEDs), including phenytoin, carbamazepine, oxcarbamazepine, and topiramate, enhance hepatic cytochrome P450 (CYP450) isoenzyme activity, increasing the catabolism of certain hormonal preparations and resulting in lower serum concentrations of these hormones. For example, patients with central adrenal insufficiency taking dexamethasone or prednisone, who are also on AEDs, may need to increase their glucocorticoid doses. This is less likely to be an issue with hydrocortisone. Because AEDs may speed up T_4 clearance and displace thyroid hormones from their binding proteins, free T_4 levels should be checked 6 weeks after starting, stopping, or switching AEDs, and LT_4 doses adjusted accordingly. Of note, phenytoin may also affect free T_4 measurements if methods other than equilibrium dialysis are used. Certain AEDs increase sex hormone–binding globulin concentrations, decreasing the bioavailability of estradiol and testosterone, potentially affecting the efficacy of gonadal hormone treatment.

22. Are there any interactions between replacement hormones?

Because GH therapy can decrease circulating free T_4 levels in adults with GH deficiency, free T_4 should be measured 6 weeks after initiation of GH replacement and after each dose escalation to rule out a mild case of central hypothyroidism. This also applies to those patients with central hypothyroidism already receiving LT_4 who are being started on GH therapy. Patients with GH deficiency have increased activity of 11-beta hydroxysteroid dehydrogenase type 1, resulting in increased conversion of cortisone to cortisol. Thus, GH replacement, by decreasing the conversion of cortisone to cortisol, may expose occult central adrenal insufficiency in patients with borderline ACTH reserve or those receiving subtherapeutic doses of glucocorticoids.

Gonadal steroids influence GH-mediated hepatic IGF-1 generation. Because oral estrogens decrease IGF-1 levels, women on estrogen replacement therapy need higher doses of GH to reach their target IGF-1 concentrations. Commencement of glucocorticoid replacement therapy can unmask central diabetes insipidus. Finally, because thyroid hormone increases the metabolic clearance rate of cortisol, initiating LT_4 in patients with coexistent but unrecognized adrenal insufficiency can precipitate an adrenal crisis.

23. Is life expectancy altered by hypopituitarism?

All-cause mortality and vascular death are increased in patients with hypopituitarism compared with age- and gender-matched controls. A recent meta-analysis concluded that the standardized mortality ratio associated with hypopituitarism in men is 2.06 (95% confidence interval [CI], 1.94–2.20] and in women is 2.80 (95% CI, 2.59–3.02). Pituitary irradiation seems to confer an increased risk of death from cerebrovascular disease.

KEY POINTS

- Anterior pituitary insufficiency, also known as hypopituitarism, is a syndrome characterized by one or more anterior pituitary hormone deficiencies due to aplasia or hypoplasia, compression, infiltration, or destruction of the hypothalamus, pituitary stalk, and/or pituitary gland.
- Most patients with hypopituitarism do not have arginine vasopressin deficiency or central diabetes insipidus, indicating that the posterior pituitary is not usually disturbed.
- The most common cause of acquired hypopituitarism is pituitary dysfunction associated with pituitary macroadenomas and/or the effect of their treatment (surgery and radiation therapy).
- If pituitary insufficiency is suspected, basal and/or dynamic pituitary function testing should be performed.
- The best biochemical indicator of thyroid replacement therapy adequacy in patients with central hypothyroidism is a free thyroxine (T_4) concentration in the mid- to upper half of the reference range.
- A dedicated pituitary magnetic resonance imaging (MRI; more slices through the sellar and parasellar regions) with and without contrast, rather than a brain MRI, should be ordered in patients with hypopituitarism, when indicated.
- Traumatic brain injury and immune checkpoint inhibitor-associated hypophysitis are increasingly recognized as causes of hypopituitarism.

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CHAPTER 24

Nonfunctioning Pituitary Tumors and Pituitary Incidentalomas

Christie G. Turin, Janice M. Kerr, and Michael T. McDermott

1. Describe the incidence pituitary adenomas.

Pituitary adenomas are benign, monoclonal neoplasms of anterior pituitary cells. A pituitary incidentaloma is a previously unsuspected pituitary lesion that is detected radiographically, for an unrelated reason. The prevalence of adenomas varies by detection method, including approximately 10% by autopsy series and approximately 20% in radiographic series. Most incidentalomas are microadenomas (>99%). Despite the prevalence of pituitary adenomas, clinically evident pituitary disease is less common, estimated at approximately 80–100 cases per 100,000 people. In most epidemiological studies, nonfunctioning adenomas (NFAs) are the second most common adenoma type after prolactinomas.

Of note, the 2022, 5th Edition of the World Health Organization (WHO) Classification of Endocrine and Central Nervous System Tumors, reclassified pituitary adenomas as pituitary neuroendocrine tumors (PitNETs). However, this term is not globally accepted by Endocrine or Pituitary Societies due to important differences in the prevalence rates and biological behavior of pituitary adenomas versus neuroendocrine tumors (e.g., indolent nature, low risk for malignant transformation with pituitary adenomas). Therefore, in this chapter, we will continue to use the term “pituitary adenoma.”

2. How are pituitary adenomas classified?

Pituitary adenomas are characterized by:

a. *Cell of Origin*: gonadotroph, lactotroph, somatotroph, corticotroph, or thyrotroph as determined by immunohistochemical (IHC) staining for the pituitary hormones and the transcription factors that determine pituitary cell lineages (e.g., T-Pit = corticotrophs, SF-1 = gonadotrophs, and Pit-1 = thyrotrophs, somatotrophs, and lactotroph cells).

b. *Size*: microadenomas <1 cm, macroadenomas ≥1 cm, and giant adenomas >4 cm.

c. *Clinical Evidence of Hormone Overproduction*: As discussed in other chapters, pituitary tumors may manifest with clinically distinct syndromes based on their hormone production (e.g., growth hormone [GH] tumors [or somatotroph adenomas] = acromegaly, adrenocorticotrophic hormone [ACTH] tumors [or corticotroph adenomas] = Cushing’s disease, prolactinomas [PRL] = galactorrhea [in females], and thyroid stimulating hormone [TSH]-secreting tumors [or thyrotroph adenomas] = secondary hyperthyroidism). In contrast, a NFA is characterized by the clinical and biochemical absence of pituitary hormone excess. The majority of NFAs are of gonadotroph origin but are not clinically apparent because of inefficient synthesis or secretion of intact follicle stimulating hormone (FSH) or luteinizing hormone (LH) molecules.

3. What is the differential diagnosis of a sellar mass?

The differential diagnosis of sellar masses is broad and includes, in relative order of frequency: pituitary adenomas, rest cell tumors (e.g., Rathke’s cleft cysts, craniopharyngiomas), arachnoid cysts, mesenchymal/stromal tumors (e.g., meningiomas, chordomas), neuronal/paraneuronal tumors (e.g., gangliocytomas, neuroblastomas), primary and secondary hypophysitis, tumors of the posterior pituitary (e.g., pituicytomas, spindle cell oncocytomas), germ cell tumors, and metastatic diseases. Importantly, normal physiologic hypertrophy, or pseudotumor, of the anterior pituitary gland can occur, such as during hypothyroidism, puberty, and pregnancy, and this can be misdiagnosed as a pituitary tumor (Fig. 24.1).

4. Describe the common presentation for nonfunctional adenomas.

NFAs comprise an estimated approximately 30% of pituitary tumors. NFAs typically occur in patients in the fifth to seventh decade of life and have a slight male predominance. The clinical spectrum of NFAs varies from being asymptomatic and detected incidentally (<1% of adenomas) to presenting with large tumors with mass effects. Delayed diagnosis is common because NFAs

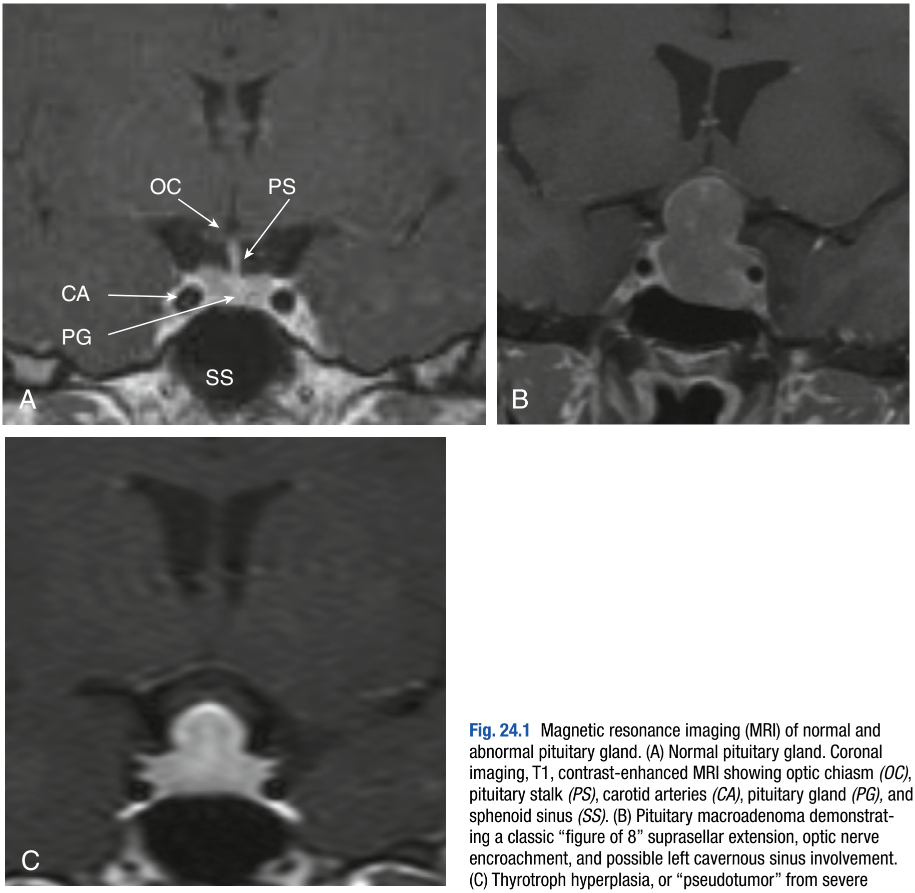
OC
PS
CA
PG
SS
A
B
C

Fig. 24.1 Magnetic resonance imaging (MRI) of normal and abnormal pituitary gland. (A) Normal pituitary gland. Coronal imaging, T1, contrast-enhanced MRI showing optic chiasm *(OC)*, pituitary stalk *(PS)*, carotid arteries *(CA)*, pituitary gland *(PG)*, and sphenoid sinus *(SS)*. (B) Pituitary macroadenoma demonstrating a classic "figure of 8" suprasellar extension, optic nerve encroachment, and possible left cavernous sinus involvement. (C) Thyrotroph hyperplasia, or "pseudotumor" from severe primary hypothyroidism.

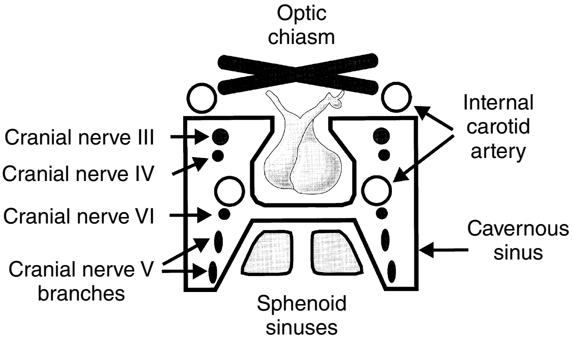
Optic chiasm
Internal carotid artery
Cranial nerve III
Cranial nerve IV
Cranial nerve VI
Cavernous sinus
Cranial nerve V branches
Sphenoid sinuses

Fig. 24.2 Schematic representation of the pituitary fossa.

lack a characteristic clinical syndrome of hormone overproduction; therefore these tumors are often macroadenomas at the time of diagnosis (80%). However, patients are often symptomatic from tumor compressive effects on nearby neurologic or vascular structures (Fig. 24.2). Common symptoms may include:

1. *Headaches:* via stretched dural membranes containing pain receptors, increased intrasellar pressure, and/or activation of trigeminal pain pathways in the cavernous sinuses.
2. *Vision Defects:* large tumors initially compress the inferior aspect of the optic chiasm and the superior nasal retinal fibers, resulting in superior temporal visual field defects. With further compression of the central portion of optic chiasm, inferior vision loss and classic bitemporal hemianopsia may occur. Depending on the pattern of tumor compression, the vision defects may be asymmetric, unilateral, or bilateral.
3. *Pituitary Hormone Deficiencies:* from interruption of pituitary-specific releasing hormone delivery through the pituitary stalk, anterior pituitary gland compression, and/or hyperprolactinemia (from stalk effect). Gonadotropins (LH, FSH) and GH are the most common deficiencies, occurring in >50% of patients. Thyroid and adrenal hormone deficiencies are less common, occurring in <30% of patients.
4. *Ophthalmoplegia/Diplopia:* from cranial nerve (CN) III (oculomotor), CN IV (trochlear), CN VI (abducens), or CN V (trigeminal) compression. Palsy of CN III is most common (presents as ptosis and 'down and out' eye position), followed by CN VI palsy (presents as convergent strabismus) and then CN IV palsy (presents as vertical diplopia).
5. *Pituitary Apoplexy:* a clinical syndrome of headache, visual deficits, ophthalmoplegia, and/or altered mental status caused by the sudden hemorrhage or infarction of the pituitary gland. It complicates an estimated 10% of pituitary adenomas.
6. *Cerebral Spinal Fluid (CSF) Leak/Rhinorrhea:* from inferior tumor extension through the dura and clivus and into the sphenoid sinus.
7. *Other Clinical Presentations:* very rarely, patients may present with (1) stroke from internal carotid artery occlusion, (2) seizures from temporal lobe involvement, and (3) intracranial hypertension and hydrocephalus from giant tumors obstructing the foramen of Monro.

5. What are the types of nonfunctioning adenomas?

Nonfunctional pituitary tumors are subtyped by IHC staining for the various pituitary hormones and the pituitary-specific transcription factors that delineate their pituitary cell lineages. NFAs constitute a heterogenous group of tumors, including:

A. Gonadotrophs (the majority of cases [80%])—stain for LHβ, FSHβ, and/or alpha subunit and/or the transcription factors SF-1 and GATA-2.
B. Silent adenomas (e.g., corticotroph adenomas—positive ACTH/T-Pit staining; somatotroph adenomas—positive GH/Pit-1 staining; or thyrotropinomas—positive TSH/Pit-1 staining) but without clinical stigmata of hormone excess.
C. Pluri-hormonal pituitary tumors (which stain for multiple pituitary hormones), although not clinically evident—positive for GH, PRL, TSHβ, α-subunit and Pit-1.
D. Null cell tumors—negative immunoreactivity for both pituitary hormones and pituitary transcription factors.

6. What is the significance of silent and pluri-hormonal pituitary tumors?

The diagnosis of a silent or a pluri-hormonal pituitary adenoma is important because of their typical aggressive behavior, high degrees of invasiveness, and high rates of recurrence. Patients with these tumors often are refractory to standard treatments and require repeat surgical resections and/or radiation treatments. In addition, a subset of silent tumors, particularly the silent ACTH or GH-secreting tumors, may later progress to functionally apparent disease, usually in association with tumor growth.

The 2017 WHO classification introduced the term "high-risk adenoma," which included certain histological subtypes, specifically silent corticotroph adenomas, pluri-hormonal PIT-1 adenomas, sparsely granulated somatotroph adenomas, Crooke cell adenomas, and lactotroph macroadenomas in men. These high-risk tumor subtypes are rare but require expectant management for disease persistence and recurrence.

7. Are nonfunctioning pituitary adenomas heritable?

Less than 5% of NFAs are associated with hereditary syndromes, or germline mutations, which include multiple endocrine neoplasia type 1 (*MEN1*) and type 4 *(MEN4)*, familial isolated pituitary adenomas (*FIPA*), or succinate dehydrogenase mutations (*SDHA*). NFAs are an uncommon manifestation of *FIPA* (<20%), but this mutation should be considered in young patients (<30 years) with large/aggressive tumors and a positive family history of pituitary adenomas.

8. Is the pathogenesis for sporadic nonfunctioning pituitary tumors known?

Analyses of sporadic NFAs have revealed interesting candidate genes including loss of tumor suppressor genes, oncogenic drivers, and epigenetic mutations. These mutations, however, are found in only a small subset of tumors.

9. How should a pituitary adenoma, including a pituitary incidentaloma, be initially evaluated?

A thorough history and physical examination can detect symptoms and/or signs of pituitary hormone excess or hypopituitarism. The Endocrine Society recommends measuring prolactin and insulin-like growth factor 1 (IGF-1) on every patient with a pituitary lesion. Screening for Cushing's disease is recommended ONLY if clinically indicated. Additional baseline pituitary hormone testing should include the following blood measurements: 8 AM cortisol, ACTH, TSH, free thyroxine (free T_4), LH, FSH, testosterone (men) and estradiol (women). In cases of macroadenomas, a DHEA-S level is also helpful in assessing for possible central adrenal insufficiency because it is the earliest adrenal marker of deficiency. Conversely, asymptomatic patients with a pituitary lesion smaller than 6 mm are unlikely to have hypopituitarism. In assessing for preoperative hypopituitarism, diagnosing and replacing thyroid hormone and glucocorticoid hormone deficiencies (as needed) should be prioritized.

10. Does an elevated serum prolactin level indicate that a tumor is a functioning prolactinoma?

No. The secretion of prolactin is negatively regulated by hypothalamic dopamine (DA) via the pituitary stalk. Stalk compression from a large NFA can impair DA delivery and thus increase prolactin levels. The serum prolactin rarely exceeds 100 ng/mL in such cases, whereas it is usually much higher with prolactin-secreting tumors (e.g., PRL levels >500 ng/ml with macroprolactinomas). In rare cases when the distinction between a prolactinoma and a NFA is difficult, a brief empiric trial of a DA agonist can be considered. The hallmarks of a NFA with hyperprolactinemia from stalk effect are that (1) the prolactin level often becomes undetectable (<1 ng/ml) on even low-dose cabergoline, and (2) the tumor does not shrink after several months of medical treatment.

11. What additional testing is needed to evaluate a pituitary adenoma?

Ideally, a high-resolution, gadolinium-enhanced, pituitary-dedicated magnetic resonance imaging (MRI) should be performed to characterize the pituitary lesion and its proximity to adjacent structures. Conversely, a contrast-enhanced computed tomography (CT) scan can be performed if the MRI is contraindicated (i.e., corporal metal, pacemakers). Compared to the normal pituitary gland (Fig. 24.1a), pituitary macroadenomas are characteristically hypoenhancing lesions on contrast-enhanced, T1-weighted MRI imaging (Fig. 24.1b). Also noteworthy, normal pituitary hyperplasia, as from severe hypothyroidism or pregnancy, can present as a "pseudotumor," which is characteristically homogenously enhancing and uniformly isointense on T1-weighted imaging (Fig. 24.1c).

Visual field testing is recommended for pituitary tumors that abut or distort the optic chiasm. Ideally, these patients should be referred to a neuro-ophthalmologist for assessment of visual acuity and visual fields. In addition, optical coherence tomography evaluation may be used to predict visual loss and outcomes.

12. What are the treatment indications and options for incidentalomas and nonfunctioning pituitary tumors?

Except for prolactinomas, functional pituitary adenomas, including incidentalomas, should be managed with transsphenoidal surgery (TSS) as first-line therapy. In addition, TSS is first-line therapy for NFAs with the following indications:

a. Symptoms of visual field deficits, vision loss, or ophthalmoplegia
b. Compression of the optic nerve on MRI
c. Endocrine dysfunction including hypopituitarism or stalk effect causing hyperprolactinemia
d. Pituitary apoplexy
e. Refractory headaches not attributable to other causes
f. Other neurological deficits related to compression from the tumor

TSS can also be considered if the tumor is close to the optic pathway or has grown significantly. Importantly, TSS should be performed by an experienced neurosurgeon who routinely performs either microscopic or endoscopic transsphenoidal techniques, and ideally as part of an expert pituitary-dedicated team (e.g., endocrinologists, neuropathologists, radiation oncologists). Lastly, radiation therapy is usually second-line therapy for a NFA if surgery is contraindicated or not desired by the patient.

13. Are there any medical therapies for nonfunctioning adenomas?

No. There are currently no effective, or FDA-approved, medical therapies for NFAs. Despite the presence of DA receptors on NFAs, the reported efficacy of DA agonists (i.e., bromocriptine and cabergoline) varies widely in the literature. In addition, there is insufficient evidence to recommend the use somatostatin receptor (SSTR) agonists (e.g., octreotide, lanreotide, pasireotide) for NFAs. Lastly, temozolomide can be considered in rare cases of very aggressive and malignant pituitary tumors.

14. How should a pituitary nonfunctioning adenoma, including a pituitary incidentaloma, be followed?

NFA/microadenomas: The recommended follow-up MRI interval varies in the literature and includes 1 year, 2 years, and 5 years (if stable in size). For stable tumor size over a 5-year period, particularly with tumors <5 mm, consideration can be given to foregoing additional imaging, unless clinically indicated. Pituitary hormone reevaluation should be considered if there has been significant interval tumor growth, or as clinically indicated. TSS is recommended for any significant interval tumor growth associated with vision defects, loss of pituitary gland function, intractable headaches, or evidence of hormone overproduction.

NFA/macroadenomas: For patients who are not treated surgically, closer MRI follow-up is required based on the risk of tumor growth. Specifically, follow-up MRI imaging at 6 months, and then annually for 5 years, is recommended. TSS is recommended for any significant interval tumor growth associated with vision defects, loss of pituitary gland function/hypopituitarism, intractable headaches, or evidence of hormone overproduction (in cases of previous "silent" tumors). For asymptomatic tumors, over a prolonged time, decreased imaging frequency (every 2–5 years) can be considered. Similarly, patients should be monitored clinically and biochemically for pituitary hormone deficiency at 6 months, and then annually (or sooner for any evidence of hypopituitarism).

15. What is the natural history of nonfunctioning pituitary tumors?

The growth frequency of NFAs is estimated to be approximately 10–13% for microadenomas and approximately 34–40% for macroadenomas over 8 years. Progressive growth usually proceeds at very slow rates (1–2 mm/year). Long term, microadenomas rarely grow to be >1 cm in size. Lastly, the incidence of pituitary apoplexy is approximately 1.1 per 100 patient-years for macroadenomas and 0.4 per 100 patient-years for microadenomas.

16. How successful is transsphenoidal surgery for nonfunctioning adenomas?

a. *TSS*: The rates of successful NFA resection vary by the tumor size and degree of invasiveness. Gross-total resection rates are highest for tumors localized exclusively in the sella but decreases to <50–60% when there is cavernous sinus invasion or bony involvement.

b. *Pituitary Hormone Function*: TSS, in experienced neurosurgical centers, maintains normal pituitary gland function in the vast majority of NFA cases, and usually improves or normalizes 15–30% of any preexisting hormone deficiencies. Patients with pituitary apoplexy, or who underwent repeat aggressive surgical resections, are unlikely to recover anterior pituitary gland function. Recovery of pituitary hormone production is best assessed at 3 months after surgery. The recommended evaluation includes basal pituitary hormone testing (as stated above) and stimulation testing (e.g., cosyntropin or GH deficiency testing) only as indicated.

c. *Headaches*: Headaches associated with a large NFA are relieved in an estimated approximately 70% of patients postoperatively.

d. *Vision*: Most patients with preoperative vision deficits improve, although many patients do not normalize their vision entirely (approximately 30% of cases). The time course of visual field recovery includes an immediate improvement in the first week postoperatively (approximately 50%), followed by a slower recovery phase over the next 6–12 months. A worse prognosis for visual recovery is associated with a longer duration of preoperative vision loss.

17. What are the risks of regrowth and treatment options for persistent/recurrent nonfunctioning adenomas?

The long-term risk of NFA regrowth after TSS is estimated to be 33–47% and 6–16% for patients with and without radiographic evidence of residual tumors, respectively, on 3-month post-TSS imaging. Risk factors for regrowth include large/invasive tumors, cavernous sinus/bony/dural involvement, and silent or pluri-hormonal NFAs. The role of proliferation markers on pathology (e.g., Ki-67 ≥3%, p53, PTTG) for predicting recurrence is not currently well defined.

For recurrent/persistent tumors, repeat TSS can be considered in select cases where there is radiological evidence for a surgically accessible sellar tumor, particularly if associated with mass effects. In general, with each subsequent neurosurgery, the likelihood for gross-total resection decreases and the risk of postsurgical complications increases. Lastly, in nonsurgical cases, radiation therapy is advised when the pituitary tumor remnants are growing significantly, or if the patient is clinically symptomatic.

18. How effective is radiation therapy for nonfunctional adenomas?

External beam radiation therapy is excellent for controlling NFA growth; >90% progression-free survival rates have been reported at 10 years in most series. Tumor control occurs regardless of the radiation technique or NFA sub-type. Two general radiation modalities are used for pituitary adenomas: (1) conventional/conformal radiation, which is delivered in daily small fractions (1.8–2.0 Gy/day) over 5–6 weeks (45–54 Gy total); or (2) stereotactic radiosurgery (SRS), which is high-dose focused radiation, delivered as photons (e.g., Gamma knife, Cyberknife, LINAC) or protons. SRS treatment typically occurs as a single treatment or during a few (2–5) sessions (fractionated stereotactic radiotherapy), with a lower total radiation dose (15–20 Gy). When feasible, SRS is generally preferred over conventional radiation because of its comparable treatment efficacy, patient convenience and possible lower rates of hypopituitarism. The choice of radiation is based on the tumor size and its proximity to the optic chiasm. Specifically, only pituitary adenomas <3 cm in size and that are at least 5 mm from the optic chiasm (because of nerve toxicity at >8 Gy doses) are considered for SRS. Lastly, small residual tumors may be monitored and not treated unless significant growth occurs.

19. What endocrine complications occur in the perioperative period?

Abnormalities of fluid and sodium balance are common after TSS because of antidiuretic hormone (ADH) dysregulation from pituitary stalk and/or posterior pituitary gland manipulation. Transient arginine vasopressin deficiency (AVP-D, formerly known as diabetes insipidus), due to impaired ADH secretion, may occur in the first 4–5 postop days in approximately 10–20% of TSS patients; AVP-D presents as high-volume urine output (>3 liters/day in adults) and frequently with hypernatremia. A second phase, which typically occurs during postop days 5–10, is characterized by the syndrome of inappropriate ADH release (SIADH), during which patients are at risk for developing hyponatremia. Rarely, permanent AVP-D develops (<2%) after ADH stores are exhausted, and only if there is significant destruction (>80–90%) of the hypothalamic ADH neurons. The classic triphasic response, AVP-D-SIADH-AVP-D, is rare, occurring in only 3–5% of patients. More commonly, isolated SIADH occurs without antecedent AVP-D (20–25%) and necessitates close follow-up during the first 2 weeks after TSS. Additional new-onset pituitary hormone deficiencies are uncommon after TSS for a NFA, particularly at experienced neurosurgery centers.

20. What is the differential diagnosis and management of postoperative polyuria?

The differential diagnosis for postoperative polyuria includes (1) fluid mobilization from perioperative fluid administration, (2) AVP-D, (3) osmotic diuresis (i.e., glycosuria), or (4) fluid mobilization after resection of a GH-secreting tumor. The hallmark of AVP-D is high-volume output (>250 mL/hour for >3 consecutive hours, or >3 L/day in adults) of dilute urine (<300 mOsm/kg, Urine Specific Gravity <1.005). Mild postoperative AVP-D can be managed with free water replacement or hypotonic fluids. More severe or persistent AVP-D cases can be treated with desmopressin (dDAVP). Desmopressin, a synthetic analogue of ADH, has the advantages over ADH of a longer half-life and reduced vasopressor activity due to amino acid substitutions. In the critical-care setting, dDAVP can be administered as a 0.25 to 0.5 mL dose (1–2 mcg), intravenously or subcutaneously, as needed to normalize urine output and plasma osmolality. Patients with persistent AVP-D symptoms at the time of hospital discharge can be treated with PRN nighttime dDAVP (starting with 0.1 mg oral tablets). Nasal spray is generally avoided shortly after surgery. Additionally, morning dDAVP dosing or further nighttime dose titration can be advised as needed for persistent, disruptive polyuria and/or nocturia. In anticipation of spontaneous recovery, patients should be counseled to periodically withhold the nighttime dDAVP dose to assess for continued need. If indicated, confirmatory testing for AVP-D can be done. Copeptin, the c-terminal segment of the ADH prohormone, can be used as a surrogate marker of ADH secretion. Different copeptin cutoff points have been validated depending on the assay used and the testing conditions (i.e., baseline versus stimulated).

21. What is the management of syndrome of inappropriate anti-diuretic hormone (SIADH)?

Hyponatremia resulting from isolated SIADH is the most common cause for 30-day rehospitalization after TSS. It occurs in upwards of 25% of TSS cases, with severe, symptomatic hyponatremia (i.e., Na ≤125 mEq/L) occurring in approximately 7% of cases. Nadir sodium levels occur most commonly between postoperative days 5–9 when patients are unmonitored at home. Fluid restriction has been the mainstay of treatment for mild SIADH for many years, and studies now support this approach in TSS patients to minimize postoperative hyponatremia and hospital readmissions. Specifically, in TSS patients without evidence of AVP-D at the time of hospital discharge, our research showed that the implementation of a 2-week 1.5 liter/day fluid restriction and a routine 1-week postoperative serum sodium level check reduced hyponatremia-related hospital readmissions by 70%. In addition, more restrictive post operative fluid regimens (i.e., 1 liter/day within the first week) have subsequently been successfully implemented at some high-volume pituitary centers, and without adverse outcomes.

The diagnosis of SIADH is based on the following criteria: serum sodium <133 mEq/L, low serum osmolality (<275 mOsm/L), inappropriately high urine osmolality (>100 mOsm/kg of water), high urinary sodium (>40 mEq with normal salt intake), euvolemic status, and normal renal function. Importantly, the evaluation of endocrinopathies associated with hyponatremia, specifically hypothyroidism and adrenal insufficiency, should be prioritized. If hospitalized, patients are routinely fluid restricted and followed closely neurologically and with serial sodium levels (every 4 hours). A urine osmolality test is recommended, at the time of admission, to assess for possible superimposed hypovolemia and/or refractoriness to fluid restriction.

For hyponatremic patients with significant neurological symptoms, such as seizures, severely altered mental status or coma, hypertonic saline (3%) should be given for a targeted serum sodium correction of approximately 1.5–2.0 mEq/L/hr for the first few hours until the serum sodium level is >120 mEq/L and symptoms are improved. In general, in cases of chronic hyponatremia (>48 hours' duration), the correction of hyponatremia should be limited to ≤12 mEq/L in the first 24 hours, and even slower correction rates (<8 mEq/L/24 h) when other risk factors are present for osmotic demyelination syndrome (e.g., liver disease, alcoholism, or poor nutritional status). Lastly, although generally not prescribed by endocrinologists, vasopressin receptor antagonists (e.g., tolvaptan or conivaptan) can be considered in cases of refractory euvolemic hyponatremia.

22. What endocrine problems may occur during long-term follow-up?

Long-term pituitary hormone deficiencies are generally only associated with recurrent tumors or radiation therapy. The risk of hypopituitarism, after conventional radiation therapy is estimated to be approximately 30–60% at 10 years and may be lower for stereotactic radiosurgery. The development of hypopituitarism generally follows a predictable pattern of hormone loss (GH ≈ LH/FSH >TSH ≈ ACTH >PRL). Posterior pituitary gland deficiencies (i.e., ADH and oxytocin) do not generally occur after radiation therapy. Expectant management for patients after radiation consists of biannual clinical assessment and biochemical testing for pituitary hormones and initiation of hormone therapy for any identified deficiencies.

TABLE 24.1 Long-Term Management of Pituitary Insufficiency

HORMONE DISORDER	MANAGEMENT
Adrenal Insufficiency	Physiological glucocorticoid replacement
Hypothyroidism	Levothyroxine replacement
Hypogonadism (men)	Androgen gels, patches, or injections
Hypogonadism (women)	Oral or transdermal contraceptives, or Postmenopausal hormone replacement
Growth Hormone	Growth hormone replacement
Arginine Vasopressin Deficiency	Desmopressin nasal spray or oral tablets

In general, physiologic hormone replacement for any resulting gonadotroph, thyrotroph, and corticotroph deficiencies, together with appropriate monitoring, is important to avoid iatrogenic endocrine complications. For example, with central hypothyroidism, the adequacy of thyroid hormone replacement is best assessed with a free T4 level (not a TSH) and should be targeted to the mid-normative range. For complete corticotroph deficiency, typical glucocorticoid replacement doses include prednisone (approximately 5 mg/day) or hydrocortisone (approximately 15–20 mg/day in two to three divided doses). Chronically higher glucocorticoid doses may result in iatrogenic Cushing's syndrome and related complications (e.g., diabetes, hypertension, osteoporosis, and metabolic syndrome). Sex steroid replacement should also be given in a physiologic and age-appropriate manner. Lastly, GH replacement is considered in adults with persistent symptoms of hypopituitarism/GH deficiency (e.g., central weight gain, fatigue, hypertension) after optimization of the other pituitary hormones.

23. Summarize the long-term management of pituitary insufficiency.

See Table 24.1.

24. Describe the presentation, diagnosis, and treatment of pituitary carcinomas.

Pituitary carcinomas are extremely rare (<0.2% of pituitary tumors) and most commonly arise from long-standing, recurrent, and invasive prolactinomas and ACTH-secreting macroadenomas. Pituitary carcinoma is defined by the presence of a pituitary tumor that is either (1) noncontiguous with the primary sellar tumor or (2) has spread to distant sites, such as spinal lesions, lymph nodes, bones, or liver. Multimodal therapy with surgery, radiation, and systemic medical therapy is often required. For patients with symptomatic mass effects, palliative tumor debulking followed by radiation therapy is usually recommended. In addition, temozolomide (TMZ), an orally active alkylating agent, has proven efficacy as monotherapy in pituitary carcinomas. A positive response to TMZ has been associated with a downregulation of the DNA-repair enzyme, O6-methylguanine-DNA methyltransferase (MGMT), although variable methods of MGMT quantitation limit its current utility. Lastly, the diagnosis of pituitary carcinoma carries a poor prognosis, with a mean survival of <4 years.

25. Which cancers metastasize to the pituitary gland?

Metastatic disease to the pituitary gland occurs in approximately 3–5% of patients with systemic carcinoma of many different types. In a systemic review of 425 published cases of pituitary metastases, the most common primary tumors metastatic to the pituitary gland were breast (37%), lung (24%), prostate (5%), renal (5%), melanoma (3%), thyroid (3%), colon (3%), and unknown primary (3%). AVP-D is the most common manifestation of metastatic disease (approximately 45%), presumably because of the direct systemic blood supply from the hypophyseal artery to the posterior pituitary gland. Additional clinical features included cranial nerve deficits/palsies (26%), anterior pituitary deficiencies (partial or total, 27%), and headaches (20%). The prognosis depends on the underlying primary tumor but is generally poor.

KEY POINTS

Nonfunctioning Pituitary Adenomas (NFAs) and Incidentalomas

- NFAs can cause symptoms primarily from mass effects, including pituitary hormone deficiencies, hyperprolactinemia, vision defects, ophthalmoplegia, and headaches.
- NFAs may elevate serum prolactin levels modestly because of pituitary stalk compression and interrupted dopamine delivery and should not be confused with a prolactinoma.
- Myriad sellar lesions can resemble a pituitary adenoma and most commonly include: Rathke's cleft cysts, craniopharyngiomas, meningiomas, and pituitary hyperplasia (pseudo-tumors).
- TSS is the first-line treatment for NFAs complicated by mass effects and for functional adenomas (except prolactinomas). Radiation therapy is considered as second-line/adjuvant therapy for incompletely resected tumors.
- NFAs and incidentalomas that do not meet criteria for surgical resection should be routinely monitored with imaging (for interval tumor growth) and repeat hormone testing.
- Silent and pluri-hormonal pituitary adenomas are characteristically aggressive, invasive, and frequently recurrent tumors that may later transform to functionally active tumors.
- Abnormalities of fluid and electrolyte balance from ADH dysregulation are common after TSS for all pituitary adenoma types. Routine fluid restriction (1–1.5 liters/day) and an outpatient serum sodium check are recommended during the early postoperative period.

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CHAPTER 25

Pituitary Stalk Lesions

Christie G. Turin and Janice M. Kerr

1. What are the function and size of a normal pituitary stalk?

The pituitary stalk, or infundibulum, anatomically connects the hypothalamus with the pituitary gland and regulates pituitary hormone secretion via the delivery of pituitary-specific releasing factors and inhibitors. In adults, the transverse and anterior–posterior diameters of a normal pituitary stalk measure approximately 3.3 ± 0.4 mm at the level of the optic chiasm and then taper to approximately 2.2 mm ± 0.4 mm at the insertion on the pituitary gland (Fig. 25.1). In general, a proximal stalk thickness ≥4 mm is abnormal. The pituitary stalk lacks a blood–brain barrier and thus enhances with gadolinium on magnetic resonance imaging (MRI). Slight deviation of the pituitary stalk is common and does not necessarily imply an underlying disease.

2. How common are pituitary stalk abnormalities?

The incidence of pituitary stalk lesions is not well characterized but generally accounts for <2% of all sellar lesions.

3. What are the main causes of pituitary stalk thickening?

The spectrum of pituitary stalk diseases is diverse and includes lesions that arise from the pituitary stalk or extend from pituitary or hypothalamic-associated tumors. The four main causes of pituitary stalk abnormalities include congenital, inflammatory, infectious, and neoplastic etiologies (Fig. 25.2).

The etiology of pituitary stalk lesions differs between children and adults and between those with or without arginine vasopressin deficiency (AVP-D, previously known as diabetes insipidus). Congenital stalk abnormalities, germ cell tumors, and Langerhans cell histiocytosis (LCH) are most likely to manifest during childhood and adolescence. Conversely, hypophysitis, Erdheim Chester disease (ECD), and many neoplasms typically present in young to middle-aged adults (21–65 years). Lastly, metastases to the pituitary gland from a wide variety of solid organ malignancies (e.g., breast, lung, prostate, renal, etc.) and central nervous system (CNS) lymphoma are more likely in older patients (>65 years).

4. What is pituitary stalk interruption syndrome?

Pituitary stalk interruption syndrome (PSIS) is characterized by an absent or thin pituitary stalk, an absent or hypoplastic anterior pituitary lobe, and/or an ectopic posterior pituitary lobe. PSIS is a frequent cause of congenital hypopituitarism (50% of cases). Patients with PSIS are usually diagnosed with hypoglycemia during the neonatal period and growth hormone deficiency during childhood. Much less commonly, it is detected in adulthood or as a sequela of traumatic brain/sheering injury. PSIS is either isolated (nonsyndromic) or associated with extra-pituitary malformations (syndromic), such as midline defects (i.e., cranio-facial abnormalities) or optic nerve hypoplasia.

5. What are the two types of hypophysitis?

Hypophysitis can be divided into primary and secondary etiologies. Primary hypophysitis is an uncommon, autoimmune condition resulting from various inflammatory cells infiltrating the pituitary gland and/or stalk. Primary hypophysitis affects an estimated 1 per 9 million people in the US and is generally more common in females. Conversely, secondary hypophysitis is caused by a diverse number of systemic inflammatory or infectious diseases, or immunotherapeutic drugs, that also result in pituitary stalk/gland inflammation.

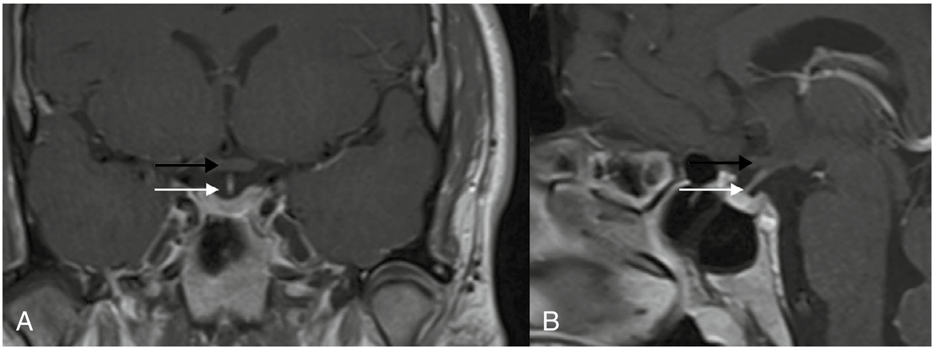

Fig. 25.1 Normal MRI of the pituitary, T1-weighted postcontrast. The pituitary gland and the infundibulum in coronal view **(A)** and sagittal view **(B)**. The infundibulum is marked at the level of the optic chiasm (*black arrow*) and at its insertion on the pituitary gland (*white arrow*).

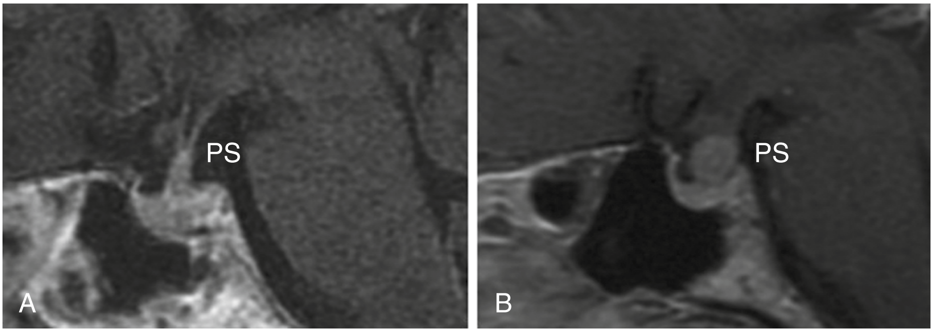

Fig. 25.2 Pituitary stalk thickening. **(A)** MRI-contrast-enhanced, sagittal view of an early pituitary stalk (PS) thickening (4 mm). **(B)** A follow-up MRI, 2 years later, showed diffuse pituitary stalk thickening (8 mm).

Anatomically, both primary and secondary hypophysitis can involve the anterior pituitary gland only (lymphocytic adenohypophysitis [LAH]), the posterior pituitary gland and stalk (lymphocytic infundibuloneurohypophysitis [LINH]), or both (lymphocytic panhypophysitis [LPH]).

6. How does hypophysitis typically present?

Clinically, patients with hypophysitis typically present with headaches (>70%), vision defects (>40%), and variable degrees of anterior pituitary hormone deficiencies (50–70%; most commonly central adrenal insufficiency followed by hypogonadism and hypothyroidism). Importantly, and unlike pituitary adenomas, AVP-D is also a common feature (>50%) with both primary and secondary hypophysitis (except for immunotherapy-related hypophysitis). On gadolinium-enhanced MRI, hypophysitis often presents with a thickened, homogenously enhancing stalk and/or a moderately enlarged pituitary gland that mimics a pituitary adenoma. Important imaging features help distinguish between hypophysitis and pituitary macroadenoma as described below (Table 25.1).

7. What are the main subtypes of primary hypophysitis?

Primary hypophysitis is subclassified by the primary inflammatory cell types into five main histological variants: lymphocytic, granulomatous, xanthomatous, IgG4-related, and mixed forms (e.g., lymphogranulomatous and xanthogranulomatous). Among these subtypes, lymphocytic hypophysitis is the most common (approximately 50–65% of all cases) and occurs predominantly in females (2–4:1 female: male ratio) and in the third decade of life. Preferential hypofunction of adrenocorticotrophic hormone (ACTH)- and thyroid-stimulating hormone (TSH)-secreting cells are frequently reported, so patients should be managed expectantly for these deficiencies.

TABLE 25.1 MRI Characteristics of Hypophysitis Versus Pituitary Macroadenomas

MRI RADIOGRAFIC FEATURES	HYPOPHYSITIS	MACROADENOMA
Asymmetric Mass	–	+
Stalk Thickening	+	–
Homogenous Enhancement with Contrast	+	–
Pituitary Gland Enlargement	+	–
Suprasellar Extension	+	+
Stalk Displacement	–	+
Loss of posterior pituitary gland hyperintensity	+ (except cancer medication-related)	–

+, more common; –, less common

Plasma cell (IgG4)-related hypophysitis (IgG4-RH), which is reviewed below, and granulomatous hypophysitis are unique diseases that can exist either in isolation or as part of a systemic disease process (e.g., sarcoidosis, granulomatosis with polyangiitis [GPA], LCH/ECD with granulomatous disease). Xanthomatous hypophysitis is considered the rarest type of primary hypophysitis and commonly presents as a cystic lesion on MRI.

In general, the diagnosis of hypophysitis is difficult, as no biomarkers, except IgG4, currently exist. In most cases, the diagnosis is presumptive based on clinical and radiographic features. If clinically indicated for progressive disease, or empiric treatment, a diagnosis can be determined by histological examination of surgical tissue. Importantly, antecedent medical treatment may obscure the pathology results.

8. What other autoimmune disorders are associated with primary hypophysitis?

Autoimmune diseases are associated with primary hypophysitis in approximately 20–25% of cases. Based on a large series of patients with primary hypophysitis (n = 376), the most commonly associated autoimmune diseases included: Hashimoto's thyroiditis (7.4%), Autoimmune polyglandular syndrome type 2 (1.8%), Graves' disease (1.6%), Systemic lupus erythematosus (1.3%), Sjogren's syndrome (0.8%), Type I diabetes mellitus (0.8%), Sarcoidosis (0.5%), Pernicious anemia (0.5%), and Addison's disease (0.5%). As such, upon the diagnosis of hypophysitis, patients with signs and symptoms of these autoimmune diseases should be screened and treated accordingly.

9. What are the natural history and treatment options for primary hypophysitis?

The natural history of hypophysitis typically involves progressive pituitary inflammation, followed by atrophy, fibrosis, and hypopituitarism. Partial spontaneous recovery of both anterior and posterior pituitary function can occur, but persistent hypopituitarism is common.

Regarding treatment options, mild cases of hypophysitis can be followed and managed expectantly. In moderate-to-severe cases of primary hypophysitis (i.e., mass effects, significant hyponatremia, etc.), an empiric trial of glucocorticoids (e.g., prednisone [or equivalent] approximately 0.6–1 mg/kg/day for 2–4 weeks followed by a taper based on treatment response) can be considered. Although high-dose glucocorticoids have historically been recommended, there is no consensus on the dose and duration of glucocorticoid therapy. Glucocorticoids can be effective in reducing mass effects, pituitary/pituitary stalk thickening, and restoring hormone deficiencies, particularly for diseases of short duration (<3–6 months), although outcome studies are lacking.

Importantly, IgG4-RH and lymphocytic hypophysitis generally have the most favorable response to steroid therapy, whereas the other inflammatory subtypes (i.e., granulomatous, xanthomatous and mixed) respond less favorably. Lastly, various other steroid-sparing, immunomodulatory agents, such as rituximab, azathioprine, and methotrexate, have been tried with variable success in patients with steroid-refractory disease.

TABLE 25.2 Diagnostic Criteria for IgG4-related Hypophysitis

DIAGNOSTIC CRITERIA	
Criterion 1: Pituitary histopathology	Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per high-power field
Criterion 2: Imaging	Sellar mass and/or thickened pituitary stalk
Criterion 3: Other organ histopathology	Biopsy-proven IgG4-related disease in other organs
Criterion 4: Elevated serum IgG4	Serum IgG4 >140 mg/dL
Criterion 5: Clinical response	Decrease in size of pituitary mass/thickened pituitary stalk and symptoms improvement with steroids
Established diagnosis if:	Criterion 1 OR Criterion 2 + 3 OR Criterion 2 + 4 + 5

10. What are Igg-4-related hypophysitis and Igg-4-related diseases?

IgG-4-related diseases (IgG4-RD) are characterized by tissue infiltration with immunoglobulin G4 (IgG4)-producing lymphocytes/plasma cells. The incidence of IgG4-RD is estimated to be 0.28–1.08/100,000 people in Japan. IgG4-RH can occur in isolation (i.e., primary hypophysitis) or, more commonly, as part of a multisystemic disease process (IgG-4 RD) (i.e., secondary hypophysitis). Interestingly, although there is a male predominance (2:1 versus females) with this disease, men typically present at an older age (sixth decade) versus females (fourth–fifth decade). In addition, isolated IgG4-RH occurs in approximately 4–5% of cases and almost exclusively in women. Conversely, men are more likely to have a greater number of organs involved with IgG4-RD. Among the extrapituitary organs affected in IgG4-RD are the pancreas (autoimmune pancreatitis), thyroid (Hashimoto's and Riedel's thyroiditis), lungs (interstitial pneumonitis), retroperitoneal fibrosis, sclerosing cholangitis, and retroorbital pseudotumor.

The diagnostic criteria for IgG4-RH are described in Table 25.2 and can be presumed without a tissue biopsy if the other criteria are met. IgG-4 RH responds to low-dose glucocorticoid therapy (e.g., prednisone 0.6 mg/kg/day), which is recommended as first-line treatment. Glucocorticoid duration and taper are generally guided by treatment response but may follow a waxing and waning course over several months. Lastly, steroid-sparing therapy with rituximab has also been successfully used, although usually as second line.

11. What are the main inflammatory causes of secondary hypophysitis?

The most common inflammatory etiologies, in addition to IgG-4 RD, and their characteristics are shown in Table 25.3. In addition, some sellar lesions (e.g., Rathke's cleft cyst, meningioma, and germinomas) can be associated with secondary inflammatory cellular reactions consistent with hypophysitis.

12. How useful are serum ACE, IgG4, and antipituitary antibody levels for diagnosing hypophysitis?

Sarcoidosis and IgG4-RH generally require a tissue sample for diagnosis. A serum or cerebrospinal fluid (CSF) ACE level is a highly specific (95%) but insensitive (25–76%) marker for neurosarcoidosis. Similarly, for IgG4 hypophysitis, elevated serum or CSF concentrations of IgG4 are found in only approximately 60–70% of patients. Lastly, investigations of antipituitary antibodies (APA) and antihypothalamus antibodies (AHA) have been studied, but these tests currently have insufficient sensitivity and specificity for diagnostic utility.

13. What are the main infectious causes of secondary hypophysitis?

Potential infectious etiologies (rare): bacterial (most commonly Gram-positive bacteria), granulomatous diseases (e.g., tuberculosis [TB], syphilis, brucellosis), fungal infections (aspergillosis, coccidioidomycosis), and Whipple's disease.

TABLE 25.3 Secondary Hypophysitis

	SARCOIDOSIS	GRANULOMATOSIS WITH POLYANGIITIS (GPA)	LANGERHANS CELL HISTIOCYTOSIS (LCH)	ERDHEIM-CHESTER DISEASE (ECD)
Age/ Gender Incidence	Young adults Black Females, 1:100,000	46 yrs. M >F = 2:1	Children (<1:200,000) >Adults	Middle age (>50s) M=F
Clinical Presentation	Multivisceral (lungs, heart, eyes, skin, sinuses), Neurosarcoidosis – 5%, Hypopituitarism/ AVP-D- 30%	Systemic vasculitis (kidneys, lungs, sinuses, otitis media), AVP-D	Children – AVP-D/ GHD Adults – AVP-D (25%) and diffuse disease (bone, skin, lungs)	Multivisceral (osteosclerosis – knees + ankles, heart, kidneys, liver, lungs, spleen, thyroid)
Evaluation (in addition to pituitary hormones)	Serum/CSF ACE, CXR, ± CT	c-ANCA, PR3-ANCA, CXR, CT	CXR, CT, Bone scan, FDG-PET, Bone marrow aspiration	Bone scan, CT
Tissue Biopsy Results	Noncaseating epithelioid-cell granulomas	Necrotizing granulomas	Langerhans / dendritic cells	NonLangerhans cell histiocytosis
Treatment	Supraphysiologic prednisone: start 1 mg/kg/d x 2 weeks	Steroids, rituximab, methotrexate	Focal vs. systemic chemotherapy and steroids, XRT	Steroids, chemotherapy, surgery, XRT, vemurafenib

ACE, Angiotensin-converting enzyme; *AVP-D*, arginine vasopressin deficiency; *c-ANCA*, cytoplasmic antineutrophil cytoplasmic antibody; *CSF*, cerebrospinal fluid; *CT*, computed tomography; *CXR*, chest x-ray; *ECD*, Erdheim-Chester disease; *FDG-PET*, fluorodeoxyglucose positron emission tomography; *GHD*, growth hormone deficiency; *GPA*, granulomatosis with polyangiitis; *PR3-ANCA*, proteinase 3-ANCA; *XRT*, radiation therapy.

Risk factors: immunocompromised patients, hematological/parasellar infections, cavernous sinus thrombosis, previous pituitary surgery.

Clinical presentation: most commonly present with mass effects (e.g., headaches, hypopituitarism, vision defects and AVP-D) and less commonly (<30%) with classic features of infection (e.g., fever, leukocytosis, meningismus).

Radiographically: pituitary abscess and TB may present as cystic lesions with gadolinium ring enhancement, although often are radiographically nondiagnostic.

Diagnosis: usually made during transsphenoidal surgical drainage.

Treatment: parental antibiotics, or antimicrobials, are generally recommended.

14. How should secondary hypophysitis be treated?

The treatment for secondary hypophysitis depends primarily on the underlying etiology and includes (1) glucocorticoids (prednisone [or equivalent]-0.6–1 mg/kg/day) for IgG-4 RD, sarcoidosis, and GPA; (2) antibiotics/antimicrobials for infectious etiologies; or (3) chemotherapy and/or radiation for LCH or ECD.

15. What immunotherapeutic agents can cause hypophysitis?

Hypophysitis is the most common immune-related adverse reaction (IRAEs) associated with the immunotherapeutic agents/immune checkpoint inhibitors used to treat various cancers (e.g., melanoma, lung, kidney, etc.). The most commonly implicated drugs are: ipilimumab, an IgG1 antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4); tremelimumab (an anti-CTLA-4 monoclonal Ab), and pembrolizumab and nivolumab, IgG4 antibodies directed against programmed cell death receptor protein (PD-1). The incidence of hypophysitis is highest for ipilimumab (12–17%) compared to the PD-1 agents (<3%). Higher rates may be associated with combination therapy. Lastly, older immunotherapy agents such as interleukin-2 and interferon have very rarely been associated with hypophysitis.

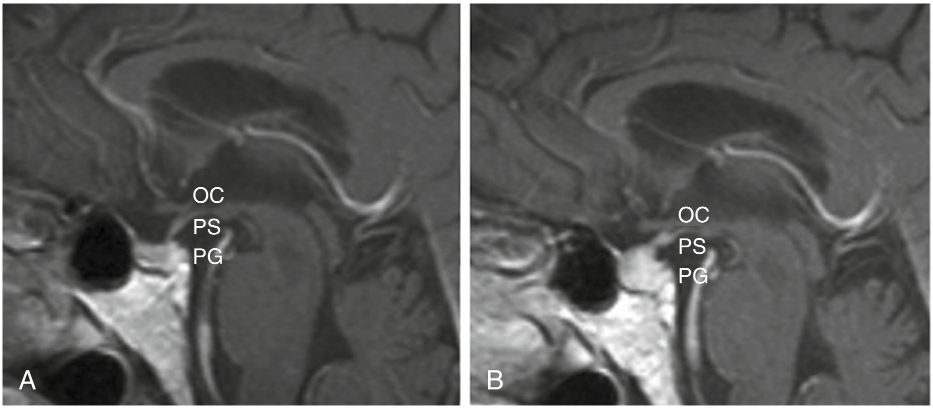

Fig. 25.3 Pituitary MRI changes with ipilimumab-induced hypophysitis. **(A)** Postcontrast sagittal view of a normal pituitary gland, including: optic chiasm (OC), pituitary stalk (PS), and pituitary gland (PG). **(B)** Postcontrast sagittal view of a pituitary gland with hypophysitis, demonstrating a hyperenhancing and enlarged pituitary stalk/gland.

16. What is the clinical presentation for immunotherapy-related hypophysitis?

The diagnosis of immunotherapy-related hypophysitis (IH), particularly when ipilimumab is used, is presumptive and based on the presence of new-onset hypopituitarism in medically treated patients, and without an alternative etiology. It is most commonly seen in older males (mean age 55 years) and after approximately 3 months (or three to four cycles) of treatment, or within 2 years of treatment. Clinically, patients present with headaches (80%), fatigue (70%), and hyponatremia (60%). Biochemically, central hormone deficiencies are commonly observed for the thyroid (90%), gonadal (85%), and adrenal (75%) axes, and less commonly for growth hormone (30%), prolactin, but not for vasopressin (AVP) (0%). The absence of AVP-D is a distinct clinical feature of IH, in contrast to other forms of hypophysitis and metastatic diseases to the pituitary gland. Radiographically, homogeneous, or heterogeneous mild pituitary gland enhancement or stalk thickening are typical features (Fig. 25.3).

On a positive note, the development of IH generally predicts a more favorable antineoplastic response to therapy, and survival is improved in ipilimumab-treated, melanoma patients, who develop IH. Similarly, patients with other malignancies (renal cell carcinoma and lung cancer) who were treated with immunotherapy and developed immune-related adverse events had a longer overall survival and progression-free survival. Immunotherapy can be temporarily paused in the setting of severe hypophysitis and can be reinitiated once the patient is clinically stable.

17. Is a biopsy necessary to distinguish immunotherapy-related hypophysitis from progressive metastatic cancer?

No. A biopsy is not recommended for IH if the condition is temporally associated with the recent initiation of therapy (i.e., after three to four cycles). In addition, unlike IH, metastatic cancer to the pituitary gland would more likely present with AVP-D.

18. What are the treatment and natural history for immunotherapy-related hypophysitis?

In general, treatment with a brief course of higher-dose steroids (i.e., predisone-1 mg/kg/day) is recommended only for hypophysitis associated with severe symptoms such as severe headaches, significant hyponatremia, or pituitary enlargement associated with optic nerve compression (or other IRAEs, like hepatitis, which may require high-dose steroids). Otherwise, physiologic glucocorticoid therapy (e.g., prednisone 5 mg/day, or hydrocortisone 15–20 mg/day) is generally recommended for mild cases, as there is no clear benefit of high-dose glucocorticoids on outcomes, survival, or pituitary gland recovery. In addition, the use of glucocorticoids does not appear to adversely affect the antitumoral response to therapy. Lastly, in addition to glucocorticoid replacement, physiologic thyroid hormone replacement, and sex steroid replacement should be initiated as indicated.

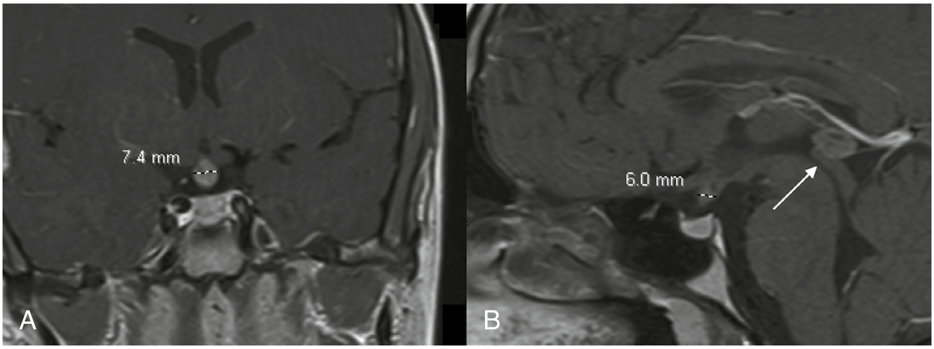

Fig. 25.4 MRI with contrast, T1-weighted images postgadolinium of a patient with bifocal germinoma. Coronal view **(A)** and noncontrasted sagittal view **(B)** showed infundibulum with focal enhancing nodular thickening along the upper aspect measuring 6.4 × 5.8 × 7.2 mm and a synchronous pineal gland mass (*white arrow*) measuring 12 × 11 × 10 mm.

Resolution of radiographic pituitary/stalk enlargement occurs in the vast majority of cases and usually within several weeks to months of onset. Regarding hypopituitarism, a portion of patients with IH may recover some anterior pituitary function, although persistent central adrenal insufficiency, central hypothyroidism, and central hypogonadism are common in an estimated 85%, 40%, and 40% of cases, respectively. Therefore patients should be management expectantly.

19. What neoplasms can cause pituitary stalk thickening?

Possible neoplastic etiologies of abnormal pituitary stalk thickening are multiple and include:

1. Craniopharyngiomas
2. Posterior Pituitary tumors: Pituicytomas, Spindle cell oncocytomas, ependymomas
3. Neuronal/para-neuronal tumors: gangliocytomas, neurocytomas, paragangliomas, neuroblastomas
4. Germ cell tumors: germinomas, mixed germ cell tumors, nongerminomatous tumors
5. Metastatic cancers: most commonly primary lung and breast cancers

20. What is an intracranial germ cell tumor?

Germ cell tumors (GCTs) account for 0.5–3% of pediatric CNS tumors in the United States. They are classified into seven histologic subtypes: germinoma, embryonal carcinoma, yolk-sac tumor, choriocarcinoma, mature teratoma, immature teratoma, teratoma with somatic-type malignancy, and mixed tumors. Some of these tumors may secrete AFP, β-hCG, or both depending on the tumor subtype. Pure germinomas do not generally cause an elevation in AFP or β-hCG. The most common sites of origin are the stalk/suprasellar region and the pineal gland. Patients with suprasellar GCTs typically present with hypothalamic/pituitary dysfunction such as AVP-D, growth hormone deficiency, central hypothyroidism, and/or central adrenal insufficiency. Although biopsy is often required for various GCTs, patients with pathognomonic, synchronous, bifocal germinomas can often forego pathological confirmation (Fig. 25.4). The treatment of patients with GCTs includes chemotherapy and radiation therapy.

21. How should patients with pituitary stalk lesions be evaluated?

Clinical/Biochemical Evaluations: A comprehensive history and physical exam should be performed, including medication review, travel history, evaluation for constitutional symptoms and examination for possible extrapituitary manifestations of systemic disease. The following biochemical evaluation, as guided by clinical context, are recommended:

1. Measurement of anterior pituitary hormones and the hormones they regulate: ACTH, 8 AM cortisol, growth hormone, insulin-like growth factor-1 (IGF-1), TSH, free thyroxine (FT4), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (men), estradiol (women) and prolactin.
2. Complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, and C-reactive protein.
3. Suspected Sarcoidosis: serum calcium, angiotensin-converting enzyme (ACE), 1,25 dihydroxyvitamin D, ± 24 hr urinary calcium excretion.

4. Suspected Germinoma: serum alpha fetoprotein (AFP) and human chorionic gonadotropin (β-hCG) levels, whole body imaging.
5. Suspected GPA (formerly Wegener's granulomatosis): cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) and proteinase 3 ANCA (PR3-ANCA), urine analysis (to evaluate hematuria/proteinuria), chest imaging.
6. Suspected TB: Quantiferon Gold in the presence of risk factors for TB (e.g., immunocompromised/HIV patients, travel to endemic areas).
7. Suspected IgG4-RH: serum or CSF IgG4 level, whole body scan.
8. Suspected LCH disease (children) or ECD (adults): radiographic skeletal survey, chest X-ray and PET-CT scans to assess for extracranial granulomas amenable to biopsy.
9. Suspected CNS lymphoma (systemic or primary-serum lactate dehydrogenase and HIV serology, CSF analysis (with flow cytometry).
10. Suspected infectious etiologies: lumbar puncture for CSF analyses, culture, and sensitivity, ± polymerase chain reaction.
11. Suspected autoimmune conditions: antithyroid peroxidase antibody (Hashimoto's thyroiditis), antinuclear antibody (systemic lupus erythematosus), antiRo/antiLa.

Imaging: Ideally, a high-resolution, thin-cut, gadolinium-enhanced, pituitary-dedicated MRI should be performed to best characterize the pituitary/stalk lesions and their proximity to adjacent structures. On MRI, the normal posterior pituitary gland is hyperintense on T1-weighted, noncontrasted images, presumably because of the vasopressin neurosecretory granules. The presence of a posterior pituitary hyperintense signal makes central AVP-D unlikely, although approximately 10–15% of normal subjects will not demonstrate a posterior gland 'bright spot' at any given time, so a negative finding does not exclude the diagnosis.

Infectious etiologies and a pituitary abscess may show a cystic or septated lesion with a thickened wall on contrast-enhanced MRI. Regarding potential extrapituitary MRI findings, neurosarcoidosis may also demonstrate periventricular lesions and leptomeningeal enhancement. Similarly, TB infections may demonstrate meningeal enhancement, intracranial abscesses, and paranasal sinus involvement. Germinomas may uniquely present with a synchronous pituitary stalk/gland lesion and a pineal gland tumor (Fig. 25.4).

Depending on the clinical context, initial biochemical evaluation and MRI findings, additional imaging with contrast-enhanced CT of the neck, chest (± chest X-ray), abdomen, and pelvis is generally recommended to evaluate for possible systemic disease and potentially identify sites for tissue biopsy. In addition, whole body fluorodeoxyglucose positron-emission tomography (FDG-PET) scans are recommended for presumed CNS lymphoma and LCH (for staging and disease monitoring).

22. How should patients with pituitary stalk lesions be followed?

For smaller pituitary stalk lesions and those not associated with immunotherapeutic drugs or significant mass effects, clinical evaluation and repeat pituitary hormone testing in 3–6 months are recommended. Pituitary MRI imaging is also recommended every approximately 6–12 months during the first 2–3 years. In general, spontaneous resolution of pituitary stalk abnormalities on MRI is most often seen with inflammatory and autoimmune conditions, whereas tumor progression is more likely with neoplasms or LCH (in children).

23. When is biopsy/resection of a pituitary stalk lesion indicated?

In general, a biopsy of the pituitary stalk lesion is recommended for the indications listed in Table 25.4.

TABLE 25.4 Indications for Biopsy of Pituitary Stalk Lesions

INDICATIONS FOR BIOSPY OF PITUITARY STALK LESIONS
1. Pituitary stalk lesions >6.5 mm
2. AVP-D and/or hypopituitarism, or progressive disease on imaging
3. If diagnosis unclear from extensive investigations and to further guide therapy
4. Lack of alternative tissue sites for biopsy

TABLE 25.5 Treatment Recommendations for Pituitary Stalk Lesions

PITUITARY STALK LESIONS	TREATMENT RECOMMENDATIONS
Congenital Lesions	• No treatment indicated • Replete deficient pituitary hormones as needed
Pituitary Stalk Neoplasms (e.g., Pituicytoma, Germinoma, Craniopharyngioma, etc.)	• Subtotal or gross-total resection, as indicated • Chemotherapy for GCT • Radiation for residual tumors • Replete deficient pituitary hormones
Hypophysitis (Primary and Secondary)	• Glucocorticoids, or alternative treatments for systemic diseases • Biopsy/decompression as indicated (Table 25.4)
Immunotherapeutic Drugs (e.g., Ipilimumab >Tremelimumab, Pembrolizumab, Nivolumab)	• High-dose glucocorticoids and temporarily withholding cancer therapy ONLY in severe hypophysitis • Otherwise, physiologic replacement of glucocorticoids and pituitary hormones deficiencies as needed • *Biopsy rarely needed*

24. How should a pituitary stalk lesion biopsy be performed?

A trans-sphenoidal surgical approach to a pituitary stalk lesion should only be performed by an experienced neurosurgeon in a high-volume pituitary center. Depending on the suspected pathology, the neurosurgical approach might include a planned gross-total resection, a subtotal/decompressive surgery, or a biopsy alone. Complete resection of a presumed inflammatory lesion from hypophysitis should be avoided because surgery is unlikely to be curative and may be associated with increased risks. Specifically, with pituitary stalk lesion resection, there is an increased risk of AVP-D, CSF leak, and hypopituitarism. In addition, approximately 10% of biopsies are nondiagnostic.

In cases of suspected pituitary stalk neoplasms in adults (e.g., pituicytoma, spindle cell oncocytoma, craniopharyngioma, etc.), the risks and benefits of a gross-total trans-sphenoidal resection versus a subtotal resection followed by radiation therapy, must be individually weighed. The goal is to control tumor growth and mass effects while preserving pituitary/hypothalamic function, whenever possible.

25. Summarize the treatment options for pituitary stalk lesions.

Due to the rarity of pituitary stalk lesions, most of the treatment recommendations are based on nonrandomized, retrospective series (Table 25.5).

KEY POINTS: PITUITARY STALK LESIONS

- In adults, a pituitary stalk thickness ≥4 mm is considered abnormal.
- The four main causes of pituitary stalk abnormalities vary by age and include: congenital, inflammatory, infectious, and neoplastic etiologies.
- Hypophysitis is divided into primary (autoimmune mediated) and secondary (systemic inflammatory, infectious, or immunotherapeutic drug–related) etiologies.
- Additional autoimmune diseases are associated with primary hypophysitis in upwards of 20–25% of cases; most commonly Hashimoto's disease, autoimmune polyglandular syndrome type 2 and Graves' disease.
- For progressive and clinically significant hypophysitis, an empiric trial of glucocorticoids or directed therapies in secondary hypophysitis are recommended.
- Ipilimumab-induced hypophysitis is the most common immune-related adverse reaction caused by immunotherapeutic cancer drugs, occurring in 12–17% of ipilimumab-treated patients.
- Immunotherapeutic-related hypophysitis, unlike most other etiologies of pituitary stalk lesions and metastatic diseases to the pituitary gland, almost never causes AVP-D but often causes persistent central adrenal insufficiency.
- A biopsy of a pituitary stalk lesion is recommended for: stalk lesions >6.5 mm, progressive tumor growth or hypopituitarism, unclear diagnosis, and lack of alternative tissue sites for biopsy. Trans-sphenoidal surgical resection can also be considered for a presumed pituitary stalk neoplasm by an experienced neurosurgeon.

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CHAPTER 26

Prolactin-Secreting Pituitary Tumors

Virginia Sarapura

1. **Describe the normal control of prolactin secretion and how it is altered in prolactin-secreting tumors?**

   Multiple factors affect prolactin secretion (Fig. 26.1). However, the principal influence on prolactin secretion is tonic inhibition by dopamine input from the hypothalamus. Dopamine interaction with receptors of the D2 subtype on pituitary lactotroph membranes activates the inhibitory G-protein, leading to decreased adenylate cyclase activity and decreased levels of cyclic adenosine monophosphate (cAMP). In prolactin-secreting pituitary adenomas, a monoclonal population of prolactin-producing cells escapes the normal physiologic input of dopamine from the hypothalamus, apparently by acquiring a peripheral blood supply. In almost all cases, responsiveness to a pharmacologic dose of dopamine is maintained.

2. **What are the normal levels of serum prolactin? Are they different in men and women? What levels are seen in patients with prolactin-secreting tumors?**

   The normal serum prolactin level is <15 or 30 ng/mL, depending on the laboratory. Women tend to have slightly higher levels than men, probably because of estrogen stimulation of prolactin secretion. In patients with prolactin-secreting tumors, the levels are usually >100 ng/mL but may be as low as 30 to 50 ng/mL if the tumor is small. A level >200 ng/mL is almost always indicative of a prolactin-secreting tumor. Very high prolactin levels may be found to be falsely normal because of the high-dose hook effect of the assay; if clinically indicated, the sample should be assayed again after dilution.

3. **What are the physiologic causes of an elevated prolactin level that must be considered in the differential diagnosis of prolactin-secreting tumors? What levels can be reached under these circumstances?**

   The most important physiologic states in which prolactin is found to be elevated are pregnancy and lactation. During the third trimester of pregnancy, the prolactin level may reach 200 to 300 ng/mL. It then gradually decreases during postpartum week 1 despite continued lactation but may continue to rise acutely at the time of breastfeeding. Prolactin values are also elevated during sleep, strenuous exercise, stress, and nipple stimulation. In these cases, the elevation is mild, <50 ng/mL.

4. **List the abnormal causes of an elevated serum prolactin value other than a prolactin-secreting tumor and state the mechanisms underlying the abnormal prolactin production.**

   See Table 26.1.

5. **What are the typical levels of serum prolactin associated with these causes?**

   The prolactin level is usually mildly elevated, 30 to 50 ng/mL, and rarely above 100 ng/mL, when the cause of the elevated prolactin is not a prolactin-secreting tumor.

6. **How does prolactin elevation result in gonadal dysfunction? What are the symptoms associated with gonadal dysfunction?**

   Elevated prolactin levels suppress the hypothalamic–pituitary–gonadal axis primarily by interfering with the secretion of gonadotropin-releasing hormone in the hypothalamus, resulting in decreased circulating levels of gonadotropins and estrogen or testosterone. Symptoms include infertility, loss of libido, menstrual irregularity and amenorrhea in women, and loss of libido and impotence in men.

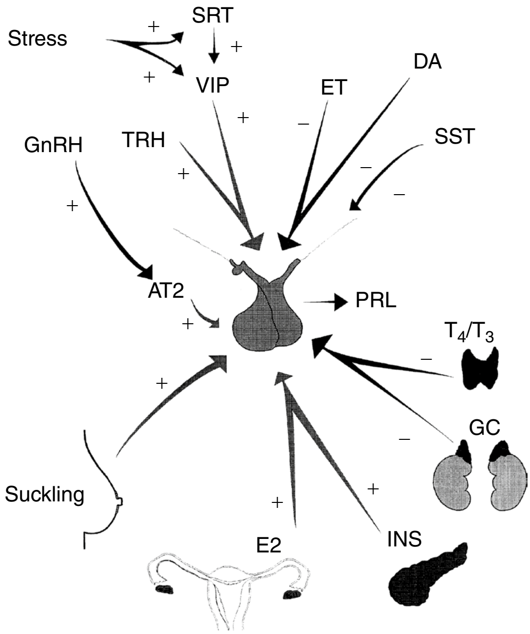

Fig. 26.1 The multiple pathways controlling prolactin secretion. Plus (+), stimulatory effect; minus (–), inhibitory effect. Input from above the pituitary gland (*depicted*) arises in the hypothalamus; input from below arises in the breast nipple, ovary, pancreas, adrenal gland, and thyroid gland, as depicted. *AT2*, Angiotensin 2; *DA*, dopamine; *E2*, estradiol; *ET*, endothelin; *GC*, glucocorticoids; *GnRH*, gonadotropin-releasing hormone; *INS*, insulin; *PRL*, prolactin; *SRT*, serotonin; *SST*, somatostatin; *T4/T3*, thyroxine/triiodothyronine; *TRH*, thyrotropin-releasing hormone; *VIP*, vasoactive intestinal peptide.

TABLE 26.1 Abnormal Causes of Elevated Serum Prolactin Level Other Than Prolactin-Secreting Tumors and Underlying Mechanism of Abnormal Prolactin Production

CAUSES	MECHANISM
Pituitary stalk interruption Trauma Surgery Pituitary, hypothalamic, or parasellar tumor Infiltrative disorders of the hypothalamus	Interference with the hypothalamic–pituitary pathways: Prolactin production increases because the tonic inhibition of prolactin secretion is interrupted; often accompanied by hypopituitarism
Pharmacologic agents: Antipsychotics Phenothiazines Tricyclic antidepressants Alpha-methyldopa Metoclopramide Cimetidine Estrogens	Specific interference with dopaminergic input to the pituitary gland
Hypothyroidism	Increased thyrotropin-releasing hormone that stimulates prolactin release
Renal failure and liver cirrhosis	Decreased metabolic clearance of prolactin; also, increased production in chronic renal failure
Intercostal nerve stimulation Chest wall lesions Herpes zoster	Mimicking of the stimulation caused by suckling

7. What is galactorrhea? Do most patients with prolactin-secreting tumors present with this symptom?

Galactorrhea is the discharge of milk from the breast not associated with pregnancy or lactation. Although a typical symptom of prolactin-secreting tumors, it may be absent in up to 50% of women, particularly when estrogen levels are very low. Galactorrhea is uncommon in men but may be seen in conjunction with gynecomastia when decreased gonadal function results in a low ratio of testosterone to estrogen.

8. Why do men with prolactin-secreting tumors often present with more advanced disease compared with women?

The major symptoms of elevated prolactin values in men are decreased libido and impotence. These symptoms may be ignored or attributed to psychological causes. Many years may go by before an evaluation is sought, often when the patient experiences headaches and visual field defects related to the mass effect of the enlarging tumor. Women are more likely to seek evaluation early in the disease process, when infertility or menstrual irregularities prompt an evaluation of their hormonal status. Interestingly, studies have suggested that large (≥10 mm) and small (<10 mm) tumors may be biologically different at their onset. There appears to be no difference in the prevalence of large tumors between men and women; however, there is a much higher prevalence of small tumors in women. This difference suggests that factors in women, possibly estrogen, may promote the appearance of prolactin-secreting tumors, but when these appear, they may be smaller and less aggressive.

9. What is the imaging technique of choice when a prolactin-secreting tumor is suspected? Why?

Magnetic resonance imaging (MRI) of the pituitary with a contrast agent, such as gadolinium, is the imaging technique of choice for the evaluation of pituitary tumors. In particular, discrimination of small tumors is improved. Computed tomography (CT) allows better visualization of bone structures, such as the floor of the sella turcica, in cases of large tumors. However, the relationship of the tumor to other soft tissue structures, such as the cavernous sinuses and carotid arteries, is best visualized with MRI. Skull radiography and tomography are not helpful.

10. Bone metabolism is altered when prolactin values are elevated. What is the mechanism for this effect? Is it reversible?

The resulting decrease in circulating estrogen or testosterone levels causes a corresponding decrease in osteoblastic bone formation and an increase in osteoclastic bone resorption. Consequently, there is a decrease in bone mineral density and progression to osteoporosis. Studies have suggested that normalization of prolactin levels restores bone density in most but not all patients, particularly those affected at an early age, before reaching peak bone mass in the third decade of life.

11. If a prolactinoma is left untreated, what is the risk of tumor enlargement?

Many longitudinal studies agree that progression of the disease is rare and occurs at a slow pace. This is particularly true of small prolactin-secreting tumors (<10 mm), <5% of which enlarge significantly over 25 years of observation. There is no reliable way to predict which tumors will show progression. Spontaneous resolution, attributed to necrosis, has also been described in some patients, particularly after pregnancy.

12. Is medical treatment available for prolactin-secreting tumors? What is the mode of action?

Medical treatment with dopamine agonists has been available since the early 1980s. The most commonly used drugs are bromocriptine and cabergoline; pergolide and hydergine are also commercially available dopamine agonists, but they are not approved by the US Food and Drug Administration specifically for treatment of prolactin-secreting tumors. Both bromocriptine and cabergoline are highly effective in reducing both prolactin levels and tumor size.

13. Describe the mode of action of dopamine agonists.

Dopamine agonists bind to the pituitary-specific D2 dopamine receptors on the cell membrane of prolactin-secreting cells, decreasing intracellular levels of cAMP and calcium. This process inhibits the synthesis and release of prolactin. An increase in cellular lysosomal activity causes involution of the rough endoplasmic reticulum and Golgi apparatus. The action of dopamine agonists on D1 dopamine receptors in the brain is the reason for the side effects of nausea and dizziness; dopamine agonists with more D2 specificity, such as cabergoline, are less likely to cause these side effects.

14. If a woman with a prolactin-secreting tumor becomes pregnant while undergoing medical treatment, should the treatment be interrupted? Should she breastfeed her infant?

Even though many studies have found that maternal treatment with dopamine agonists is safe for the fetus, it is recommended that the drug be stopped as soon as pregnancy is diagnosed. The risk of tumor expansion is low, <5% for small prolactin-secreting tumors and 15% to 35% for large tumors. Assessment of symptoms, particularly headaches, and visual field tests should be performed every 1 to 3 months; any evidence of tumor reexpansion should prompt the reinstitution of treatment. Breastfeeding does not appear to add any significant risk for these patients, but close follow-up should be continued. Once breastfeeding ends, the prolactin level should be measured 2 to 3 months later and treatment with a dopamine agonist should be restarted if the prolactin level is high.

15. How long does it take for medical treatment to reduce the serum prolactin level? To reduce the size of the tumor?

The onset of action of dopamine agonists is rapid; because prolactin has a serum half-life of 50 minutes, a decrease in the prolactin level may be noted within 2 hours. However, normalization of prolactin levels may take weeks or months, with the maximal decrease usually seen by 3 months. Tumor size reduction can occur within 48 hours and may be demonstrated by improvement in visual fields when these are affected by the tumor. Tumor shrinkage is usually evident by 3 months; for larger tumors, and it is recommended that MRI be performed again at this time to ensure that there is an adequate response to the treatment. Maximal tumor shrinkage, however, is not usually observed until after at least 12 months of treatment. Repeat MRI after 1 year of treatment is, therefore, recommended.

16. How long is medical treatment of prolactin-secreting tumors required? Why?

Lifelong treatment is usually required because prolactin levels rise and tumors reexpand when treatment is interrupted, suggesting that the effect is mostly cytostatic. More recent reports, however, suggest that approximately 20% of cases may be cured after 2 to 5 years of treatment (longer time may be required for larger tumors), and some evidence suggests that dopamine agonists may have a cytolytic effect in these cases.

17. When is surgical removal of a prolactin-secreting tumor indicated?

With the availability of dopamine agonists, surgery has become a secondary choice in the treatment of prolactin-secreting tumors, particularly since the long-term surgical cure rate for large tumors is only 25% to 50%. The principal indications for surgical treatment of a prolactin-secreting tumor are intolerance or resistance to dopamine agonists and acute hemorrhage into the tumor. A cerebrospinal fluid leak resulting from erosion of the floor of the sella turcica is another indication for surgical debulking and repair. Surgical resection of smaller, noninvasive prolactinomas may be considered if done by an experienced neurosurgeon.

18. When is radiotherapy indicated to treat a prolactin-secreting tumor?

Radiotherapy has rarely been used because hypopituitarism is a common side effect, generally occurring within a few years. This complication is of critical concern, particularly in patients undergoing treatment for infertility. However, radiotherapy may be a useful adjunct in patients who require additional treatment after surgery and who do not tolerate dopamine agonists. Some experts advocate the use of radiotherapy 3 months before attempting pregnancy in women with large tumors to avoid tumor reexpansion during pregnancy. Stereotactic radiosurgical techniques, such as the gamma knife, may improve outcomes and minimize radiation side effects.

19. What is a giant prolactinoma?

Giant prolactinomas are defined as prolactinomas >4 cm in size. Cabergoline is usually the initial treatment of choice, although high doses may be required; surgery is indicated for cabergoline-resistant cases, and radiation therapy can be added if the tumor progresses. If progression continues despite these measures, temozolomide, an alkylating agent that depletes a DNA repair enzyme, may be considered.

20. Are prolactinomas ever malignant?

Malignant prolactinomas account for about 1 to 2 per 1000 pituitary adenomas. Features that may suggest malignancy are loss of responsivity to dopamine agonists in a previously responsive tumor, rapid regrowth after surgery, repeated operations for tumor growth and rising prolactin levels, the development of metastases, and high Ki-67 labeling. Aside from surgery, other treatment measures that may be effective are radiation therapy and/or temozolomide, an alkylating agent that depletes a DNA repair enzyme.

KEY POINTS

Prolactin-Secreting Pituitary Tumors

- When a mild prolactin elevation is found (30–50 ng/mL), physiologic, pathologic, and iatrogenic causes must be excluded before the diagnosis of a small prolactin-secreting tumor can be made.
- A prolactin level >200 ng/mL is almost always indicative of a prolactin-secreting tumor, except during pregnancy.
- Elevated prolactin values cause galactorrhea and suppress the hypothalamic–pituitary–gonadal axis, resulting in hypogonadism and a progressive decrease in bone mineral density.
- Untreated prolactin-secreting tumors usually grow very slowly; <5% of small tumors are noticeably larger after 2 to 5 years.
- Treatment with dopamine agonists is well tolerated and quickly effective in normalizing the prolactin level and shrinking the tumor mass of even very large prolactin-secreting tumors.

WEBSITES

1. National Institute for Diabetes, Digestive and Kidney Disorders: https://www.niddk.nih.gov/health-information/endocrine-diseases/prolactinoma
2. UpToDate: https://www.uptodate.com/contents/high-prolactin-levels-and-prolactinomas-beyond-the-basics
3. Cleveland Clinic: https://my.clevelandclinic.org/health/diseases/22007-prolactinoma

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Growth Hormone–Secreting Pituitary Tumors

Mary H. Samuels

1. What is the normal function of growth hormone (GH) in children and adults?

In children, GH is responsible for linear growth. In children and adults, GH has many effects on intermediary metabolism, including protein synthesis and nitrogen balance, carbohydrate metabolism, lipolysis, and calcium homeostasis.

2. How are levels of GH normally regulated?

Pituitary secretion of GH is primarily regulated by two hypothalamic hormones: stimulatory GH-releasing hormone (GHRH) and inhibitory somatostatin. Secretion of GH is also affected by adrenergic and dopaminergic hormones, as well as by other central nervous system and peripheral factors. GH is secreted from the pituitary gland in pulses and has a short plasma half-life, so GH levels can vary markedly with repeated measurements in healthy as well as disease states.

3. Does GH directly affect peripheral tissues?

In most cases, no. Most effects of GH are mediated by another hormone called insulin-like growth factor-1 (IGF-1). IGF-1 is made by the liver and other organs in response to stimulation by GH. IGF-1 feeds back to the pituitary gland and suppresses GH secretion. Unlike GH, IGF-1 has a long half-life in plasma; thus, plasma IGF-1 levels are generally more helpful than GH levels in the diagnosis of GH abnormalities.

4. What are the clinical features of excessive production of GH in children?

In children who have not yet undergone puberty and whose long bones still respond to GH, excessive GH causes accelerated linear growth. The result is gigantism.

5. Describe the clinical features of excessive production of GH in adults.

In adults, excessive GH causes acromegaly. Acromegaly is rare, with an incidence of approximately four cases per million people per year, and often progresses gradually and insidiously. The pathologic and metabolic effects of acromegaly are summarized in Table 27.1.

6. What is the single best clue in examining a patient suspected of having acromegaly?

An old driver's license picture or other old photographs provide the best clues. Patients with acromegaly are often unaware of the gradual disfigurement caused by the disease or attribute it to aging. Comparing serial photographs can help establish the diagnosis and date its onset. Unfortunately, due to the gradual onset of symptoms, the diagnosis of acromegaly is delayed for an average of 5–6 years, by which time patients present with more advanced disease.

7. What is the cause of death in patients with acromegaly?

Acromegaly increases cardiovascular and metabolic risk factors, including hypertension, glucose intolerance, cardiomyopathy, and sleep apnea. It also increases the risks of a number of cancers. In the past, the mortality from inadequately treated acromegaly was about double the expected rate in healthy age-matched subjects. Improved treatment has decreased this risk, but there is still a 30% increased risk of mortality in patients with acromegaly. In the past, the major cause of death was due to cardiovascular disease. With better treatment of associated cardiovascular risk factors, cancer-related deaths are now more common.

8. The husband of a patient with acromegaly complains that he cannot sleep because his wife snores. Is this relevant?

Sleep apnea occurs in 50% to 70% of patients with acromegaly. It can result from soft tissue overgrowth of the upper airway or to altered central respiratory control. Sleep apnea may

TABLE 27.1 Clinical Effects of Acromegaly

CLINICAL EFFECT	CAUSE
Coarse features	Periosteal formation of new bone
Enlarged hands and feet	Soft tissue hypertrophy
Excess sweating	Hypertrophy of sweat glands
Deepened voice	Hypertrophy of larynx
Skin tags	Hypertrophy of skin
Upper airway obstruction and sleep apnea	Hypertrophy of tongue and upper airway, central respiratory depression
Osteoarthritis	Hypertrophy of joint cartilage and osseous overgrowth
Carpal tunnel syndrome	Hypertrophy of joint cartilage and osseous overgrowth
Hypertension, hypertrophic cardiomyopathy, congestive heart failure	Cardiac hypertrophy
Hypogonadism	Multifactorial
Diabetes mellitus, glucose intolerance	Insulin antagonism, other factors
Colonic polyps	Colonic hypertrophy

contribute to morbidity and mortality in acromegaly by producing hypoxia and pulmonary hypertension.

9. If you suspect that a patient may have acromegaly, what test should you order?

The single best screening test for acromegaly is the plasma level of IGF-1. Age- and sex-specific normal ranges should be used to interpret IGF-1 levels. Unlike GH levels, which are pulsatile and higher at night, samples can be drawn any time of day. In adults, acromegaly is essentially the only condition that causes elevated IGF-1 levels. In children, IGF-1 levels are more difficult to interpret because growing children normally have high levels. IGF-1 levels may be less accurate in mild acromegaly, malnutrition, hepatic or renal disease, pregnancy, severe obesity, uncontrolled diabetes mellitus, or oral estrogen therapy.

10. The patient's IGF-1 level is not elevated, but you still think that she may have acromegaly. What other test should you order?

The gold-standard test to rule out acromegaly is the measurement of serum GH levels in the fasting state and after glucose suppression. Healthy subjects suppress GH levels 2 hours after an oral glucose load (75 g), whereas patients with acromegaly show insufficient suppression in GH levels. The cutoff for an abnormal GH response to an oral glucose load is 0.4–1.0 mcg/L, depending on the sensitivity of the GH assay. This test should be performed if the IGF-1 is normal or only slightly elevated in a patient with suspected acromegaly. It may be unreliable in patients with diabetes mellitus, hepatic or renal disease, severe obesity, pregnancy, or in patients receiving estrogen therapy.

11. After the biochemical diagnosis of acromegaly or gigantism is made, what is the next step?

Excessive secretion of GH is almost always caused by a benign pituitary tumor. Therefore the next step is to obtain a radiologic study of the pituitary gland. The optimal study is magnetic resonance imaging (MRI) with special cuts through the pituitary gland. MRI can help assess tumor size, location, and invasiveness, which are all important for the pituitary surgeon.

12. What causes GH-secreting pituitary tumors?

GH-secreting pituitary tumors are monoclonal and are almost always sporadic, indicating that a spontaneous somatic mutation is a key event in neoplastic transformation of somatotrophs. Further studies have clarified the nature of the mutation in some GH tumors that have an altered

TABLE 27.2 Endocrine Syndromes Associated With Acromegaly

SYNDROME	MAJOR INVOLVED ORGANS	CLINICAL FINDINGS	OTHER CLUES
Multiple endocrine neoplasia type 1 and 4 (MEN 1, MEN 4)	Pituitary tumors Parathyroid hyperplasia Islet cell tumors	Hypercalcemia (most) Peptic ulcer disease (if gastrinoma) Hypoglycemia (if insulinoma)	Autosomal dominant Check calcium levels in patients with acromegaly
McCune-Albright syndrome	Bones Skin Gonads Others	Polyostotic fibrous dysplasia Café-au-lait spots Sexual precocity	Mostly in girls
Carney's complex	Heart Skin Adrenals Others	Cardiac myomas Pigmented skin lesions	
Pigmented nodular adrenal hyperplasia	Many other tumors		Autosomal dominant

stimulatory subunit (G_S) of the G-proteins that regulate adenylate cyclase activity. In a mutated cell, alterations in the G_S subunit cause autonomous adenylate cyclase activity and elevated secretion of GH. However, the mutant G_S is only found in about 40% of patients with acromegaly. The mechanism of GH regulation and tumor growth differs in other patients with acromegaly.

13. Are some GH-producing tumors more aggressive than others, and is there a way to tell?

GH-producing tumors causing acromegaly are almost always benign but can be locally invasive and show progressive growth. They are often characterized histologically as being densely granulated or sparsely granulated. Sparsely granulated GH-producing tumors are less well-differentiated tumors, are generally more locally aggressive, respond less well to somatostatin analogues, and have a worse prognosis.

14. Are other endocrine syndromes possible in patients with acromegaly or gigantism?

Yes. Otherwise acromegaly and gigantism would not be endocrine disorders. Table 27.2 lists endocrine syndromes that include acromegaly.

15. Do other tumors besides pituitary tumors make GH and cause acromegaly or gigantism?

Yes. Rare tumors of the pancreas, lung, ovary, and breast may produce GH.

16. Do tumors ever cause acromegaly or gigantism by making excessive GHRH?

Yes. Rare cases of GHRH production by various tumors have been described in the lung, gastrointestinal tract, or adrenal glands. They cause acromegaly by stimulating pituitary secretion of GH. The clinical and biochemical features of acromegaly are indistinguishable from those of acromegaly caused by a pituitary adenoma. Pituitary enlargement also occurs as a result of hyperplasia of somatotrophs. Some patients have had inadvertent transsphenoidal surgery (TSS) before the correct diagnosis was made. Therefore the plasma level of GHRH should be measured in patients with acromegaly who have an extrapituitary abnormality or hyperplasia on pituitary pathology.

17. If MRI of the pituitary confirms a tumor in the patient with acromegaly, what issues other than the metabolic effects of excessive GH should be considered?

1. *Is the tumor making any other pituitary hormones besides GH?* For example, many GH-secreting tumors also produce prolactin; rare tumors also make thyroid-stimulating hormone or other pituitary hormones. In patients with acromegaly, prolactin levels should be measured, as well as other hormones when clinically indicated.

2. *Is the tumor interfering with the normal function of the pituitary gland?* Specifically, does the patient have impaired thyroid, adrenal, and/or gonadal function? Does the patient have diabetes insipidus? It is important to diagnose and treat pituitary insufficiency before therapy for the excessive secretion of GH, especially if the patient is scheduled for surgery.
3. *Is the tumor causing effects owing to its size and location?* Possible effects include headache, visual field disturbances, and extraocular movement abnormalities. Formal visual fields examination should be carried out in patients with large pituitary tumors.

18. How big are GH-secreting pituitary tumors?

GH-secreting tumors vary considerably in size, but over 70% are >1 cm in diameter when diagnosed (i.e., macroadenomas), and some can be very large. Tumor size is an important issue because it determines success rates of treatment.

19. What is the primary treatment for acromegaly or gigantism?

Goals of therapy for GH-secreting tumors include reduction of mortality risk, tumor shrinkage, and control of GH hypersecretion. Numerous studies have shown that the strongest predictor of patient outcomes and mortality is biochemical control of excess GH secretion. The treatment of choice for GH-secreting tumors is TSS performed by an experienced pituitary surgeon. The primary predictors of surgical remission are tumor size and invasiveness of surrounding structures, especially the cavernous sinuses. Surgical expertise is another major predictor of remission; in experienced hands, remission is more common. Most patients with microadenomas are cured (80–90% in referral centers), while surgical cure rates with macroadenomas are lower but still substantial (50–75% in referral centers). Significant reduction in GH levels and improvement in symptoms typically follow surgery, even if cure is not obtained and further treatment is required. In experienced hands, surgical complications are unusual but can include hypopituitarism, transient or permanent diabetes insipidus, and cerebrospinal fluid leakage. Certain patients may benefit from medical therapy before surgery to reduce surgical risks, including patients with congestive heart failure, severe sleep apnea, intubation problems, or other comorbidities of acromegaly. There are no conclusive data that preoperative treatment improves cure rates, however.

20. What are the options for medical therapy of acromegaly?

If GH-secreting tumors are not controlled by surgery alone, adjuvant therapy is indicated. Medical therapy is also indicated for patients who are poor surgical candidates or who refuse surgery. There are three drug classes available for the treatment of acromegaly: somatostatin receptor ligands (SRLs) (octreotide, lanreotide, pasireotide); the GH receptor antagonist pegvisomant; and dopamine agonists (cabergoline, bromocriptine). In patients with significant residual disease after surgery, either an SRL or pegvisomant is recommended as the first-line medical therapy. In patients with modest residual disease, an initial trial of a dopamine agonist may be appropriate, although the response to cabergoline appears to decrease with time. When patients do not respond adequately to single agents, combination therapy with two or all three of these agents may improve efficacy and reduce side effects.

21. Discuss the mechanism of action of SRLs.

Most GH-secreting tumors have somatostatin receptors and respond to exogenous somatostatin with decreases in GH levels. The development of long-acting SRLs (octreotide long-acting release [LAR], lanreotide, pasireotide LAR) was a major advance in the treatment of acromegaly. Pasireotide LAR appears to be more effective than the other two agents but carries additional side effects (see below).

22. How effective are SRLs?

SRLs markedly decrease GH levels in most patients, with alleviation of many of the symptoms and side effects of acromegaly. Approximately 35% to 55% of patients receiving SRLs achieve biochemical remission, although additional patients experience symptomatic improvement with partial biochemical responses. Significant tumor shrinkage occurs in approximately 60% of patients. However, these agents do not cure acromegaly; stopping the drug usually leads to increases in GH levels and tumor regrowth. SRLs are commonly used indefinitely after surgery has failed to achieve biochemical control of GH hypersecretion. They can also be used before surgery to improve comorbidities, after surgery while waiting for radiation therapy to take effect (see below), or instead of surgery in carefully selected patients. Common side effects include gastrointestinal symptoms and gallstone formation. Octreotide LAR and lanreotide usually have minimal effects on glucose metabolism, but can cause mild hyperglycemia. In contrast, pasireotide causes hyperglycemia in up to 70% of patients and diabetes mellitus in 25–40%, and so is generally reserved for patients who do not respond adequately to the other SRLs.

23. Describe the mechanism of action of pegvisomant.

Pegvisomant is a human GH receptor antagonist that competes with endogenous GH for binding to its receptor and blocks production of IGF-1. This improves the clinical effects and metabolic defects in acromegaly. Pegvisomant controls IGF-1 levels in about 70% of patients. It does not appear to affect tumor size in the great majority of patients, but tumor size should be monitored, given the drug's mechanism of action. It is mainly used in patients who are resistant to or do not tolerate SRLs, or in combination with SRLs to improve biochemical control. It can also be used as primary medical therapy, with a recent study reporting a 70% biochemical control rate. The main side effect of pegvisomant is liver function abnormalities, which are usually transient. Note that IGF-1 remains an accurate biomarker for acromegaly control in pegvisomant-treated patients, but GH levels cannot be monitored because of the persistence of GH hypersecretion.

24. What about radiation therapy for acromegaly?

Radiation therapy of GH-secreting tumors causes a gradual decline in GH levels over many years, and is therefore generally reserved as a third-line therapy for acromegaly. It may also increase the long-term risk of mortality. Stereotactic radiotherapy had increasingly replaced conventional radiation therapy, as it may be more effective and work more quickly for pituitary tumors. However, stereotactic radiotherapy still takes months to years to work. Radiation therapy leads to the arrest of tumor growth in most patients and biochemical control in 50–60% of patients over time. Many patients eventually develop hypopituitarism from radiation therapy, and there may also be small risks of vision deficits, secondary tumors, cerebrovascular events, or cognitive effects.

25. How can one tell whether a patient has been cured of acromegaly?

Older studies defined cure as a random GH level <5 mcg/L. More recent studies have shown that this criterion is inadequate, and more rigorous criteria have been developed as GH assays have become more sensitive. For complete control of GH secretion, patients should have normal age- and sex-adjusted IGF-1 levels and GH levels following an oral glucose load of <1.0 mcg/L (older GH assays) or <0.4 mcg/L (more sensitive GH assays). Note that GH nadirs after an oral glucose load can be affected by age, body mass index, sex, oral estrogens, glucose intolerance, and diabetes, so results must be interpreted with these issues in mind. Finally, there is significant variability in IGF-1 assays, and it is recommended that the same assay be used throughout a patient's follow-up.

26. The patient has undergone TSS for acromegaly and now has normal IGF-1 and GH levels, as well as suppressed levels of GH after oral glucose administration. How should the patient be monitored?

It appears that the patient is cured, but GH tumors can slowly regrow over years. At the least, measurements of GH and IGF-1 should be repeated every 6 to 12 months. Some physicians measure GH levels after glucose administration as well. Tumor mass should be monitored at intervals with pituitary MRI. The patient also requires an evaluation for colonic neoplasia, as studies show that about one-third of patients with acromegaly have premalignant colonic lesions. In addition, it is important to assess whether the surgery damaged normal pituitary function by evaluating the patient's thyroid, adrenal, gonadal, and posterior pituitary function. The effects of surgery on visual fields should be assessed, especially if the patient had preoperative defects.

27. The patient asks which symptoms and physical abnormalities will improve after cure is confirmed. What is the appropriate answer?

Most soft tissue changes improve, including coarsening of facial features, increased size of hands and feet, upper airway hypertrophy, carpal tunnel syndrome, osteoarthritis, and excessive sweating. Hypertension, cardiovascular disease, sleep apnea, diabetes, rates of vertebral fractures, and quality of life also improve, although some comorbidities may require additional management. Unfortunately, bony overgrowth, damage to joints, and structural heart changes do not regress after treatment.

28. For bonus points, name an actor with acromegaly and the movie in which he starred.

André René Roussimoff, popularly known as Andre the Giant, starred as Fezzik in *The Princess Bride*.

KEY POINTS

Acromegaly

- Acromegaly leads to gradual soft tissue enlargement and disfigurement over many years, and the patient may be unaware of the changes.
- Acromegaly causes damage to bones, joints, the heart, and other organs and is associated with considerable morbidity and excess mortality.
- The best screening test for acromegaly is measurement of insulin-like growth factor type 1 level.
- The best initial treatment for acromegaly is usually transsphenoidal surgery, performed by an experienced pituitary surgeon.
- There are adjuvant medical treatments for acromegaly that are effective in controlling the metabolic effects of excess growth hormone secretion.

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Cushing's Syndrome

Mary H. Samuels

1. Describe the normal function of cortisol in healthy people.

Cortisol and other glucocorticoids have many effects as physiologic regulators. They increase glucose production, inhibit protein synthesis and increase protein breakdown, stimulate lipolysis, and affect immunologic and inflammatory responses. Glucocorticoids are important for maintenance of blood pressure and form an essential part of the body's response to stress.

2. How are cortisol levels normally regulated?

Adrenal production of cortisol is stimulated by the pituitary hormone adrenocorticotropin (ACTH). ACTH production is stimulated by the hypothalamic hormones corticotropin-releasing hormone (CRH) and vasopressin (ADH). Cortisol feeds back to the pituitary and hypothalamus to suppress levels of ACTH and CRH. Under nonstress conditions, cortisol is secreted with a pronounced circadian rhythm, with higher levels early in the morning and lower levels late in the evening. Under stressful conditions, secretion of CRH, ACTH, and cortisol increases, and the circadian variation is blunted. Because of the wide variation in cortisol levels over 24 hours and appropriate elevations during stressful conditions, it may be difficult to distinguish normal secretion from abnormal secretion. For this reason, the evaluation of a patient with suspected Cushing's disease is often complex and confusing.

3. What are the clinical symptoms of excessive levels of cortisol?

Prolonged and inappropriately high levels of cortisol lead to Cushing's syndrome, characterized by:

- Obesity, especially central (truncal) obesity, with wasting of the extremities, moon facies, supraclavicular fat pads, and "buffalo hump"
- Thinning of the skin, with facial plethora, easy bruising, and violaceous striae
- Muscular weakness, especially proximal muscle weakness, and atrophy
- Hypertension, atherosclerosis, congestive heart failure, and edema
- Gonadal dysfunction and menstrual irregularities
- Psychological disturbances (e.g., depression, emotional lability, irritability, sleep disturbances)
- Osteoporosis and fractures
- Increased rate of infections and poor wound healing

4. All of my clinic patients look like they have Cushing's syndrome. Are some clinical findings more specific for Cushing's syndrome than others?

Some manifestations of Cushing's syndrome are common but nonspecific, whereas others are less common but quite specific. The clinical findings are listed in Table 28.1, with the more specific findings listed first, followed by the more common but less specific findings.

5. A patient presents with a history of obesity, hypertension, irregular menses, and depression. Does she have excessive production of cortisol?

Excessive cortisol is highly unlikely. Although the listed findings are consistent with glucocorticoid excess, they are nonspecific; most patients with such findings do not have Cushing's syndrome (see Table 28.1). True Cushing's syndrome is uncommon, with an incidence of two to three cases per million people per year, although it may be higher in patients with hypertension, diabetes, osteoporosis, or incidental adrenal masses. The diagnosis of Cushing's syndrome is often delayed for years due to the nonspecific nature, gradual progression of the presenting symptoms and signs, and complexities of testing.

TABLE 28.1 Symptoms and Signs of Cushing's Syndrome

MORE SPECIFIC, LESS COMMON	MORE COMMON, LESS SPECIFIC
Easy bruising, thin skin (in young patient)	Hypertension
Facial plethora	Obesity/Weight gain
Violaceous striae	Abnormal glucose tolerance or diabetes mellitus
Proximal muscle weakness	Depression, irritability
Hypokalemia	Peripheral edema
Osteoporosis (in young patient)	Acne, hirsutism
	Decreased libido, menstrual irregularities

6. The patient also complains of excessive hair growth and has increased terminal hair on the chin, along the upper lip, and on the upper back. Is this finding relevant?

Hirsutism is a common, nonspecific finding in many female patients. However, it is also consistent with Cushing's syndrome. If it is caused by Cushing's syndrome, hirsutism results from excessive production of adrenal androgens under ACTH stimulation. Thus, hirsutism in a patient with Cushing's syndrome is a clue that the disorder is caused by excessive production of ACTH. (The only other condition associated with excessive production of glucocorticoids and androgens is adrenal cancer, which is usually obvious on presentation.)

7. The patient also has increased pigmentation of the areolae, palmar creases, and an old surgical scar. Are these findings relevant?

Hyperpigmentation is a sign of elevated production of ACTH and related peptides by the pituitary gland. It is uncommon (but possible) in Cushing's syndrome caused by benign pituitary tumors because levels of ACTH do not usually rise high enough to cause hyperpigmentation. It is more common in the ectopic ACTH syndrome because ectopic tumors produce more ACTH and other peptides. The combination of Cushing's syndrome and hyperpigmentation may be an indication of a serious condition.

8. What is the cause of death in patients with Cushing's syndrome?

Patients with inadequately treated Cushing's syndrome have a markedly increased mortality rate (two- to fivefold above normal), usually from cardiovascular disease, thromboembolic events, or infections. Hypertension, impaired glucose tolerance, dyslipidemia, and visceral obesity all contribute to the excess risk for cardiovascular mortality. This excess mortality risk improves with adequate therapy, but may persist.

9. What causes Cushing's syndrome?

Cushing's syndrome is a nonspecific name for any source of excessive glucocorticoids. There are four main causes, which are further detailed in Table 28.2:

1. Exogenous glucocorticoids (ACTH independent)
2. Pituitary Cushing's syndrome (ACTH dependent). This is referred to as Cushing's disease.
3. Ectopic production of ACTH (ACTH dependent)
4. Adrenal tumors (ACTH independent)

10. Of the various types of Cushing's syndrome, which is the most common?

Overall, exogenous Cushing's syndrome is most common. It rarely presents a diagnostic dilemma because the physician usually knows that the patient is receiving glucocorticoids. Of the endogenous causes of Cushing's syndrome, pituitary Cushing's syndrome (Cushing's disease) accounts for about 70% of cases. Ectopic secretion of ACTH and adrenal tumors cause approximately 15% of cases each (see Table 28.2).

11. Do age and gender matter in the differential diagnosis of Cushing's syndrome?

Of patients with Cushing's disease (pituitary tumors), 80% are women, whereas the ectopic ACTH syndrome is more common in men. Therefore, in a male patient with Cushing's syndrome, the risk of an extrapituitary tumor is increased. The age range in Cushing's disease is most

TABLE 28.2 Causes of Cushing's Syndrome and Their Relative Frequency

ACTH DEPENDENT (80%)	ACTH INDEPENDENT (20%)
Pituitary (85%)	Adrenal tumors
Corticotroph adenoma	Adrenal adenoma
Corticotroph hyperplasia (rare)	Adrenal carcinoma (rare)
Ectopic ACTH syndrome (15%)	Bilateral macronodular adrenal hyperplasia (rare)
Small cell lung carcinoma (50%)	Primary pigmented nodular adrenal disease (rare)
	Carney's complex (rare)
Foregut tumors (35%)	Exogenous glucocorticoids (common)
Bronchial carcinoid	Therapeutic (common)
Thymic carcinoid	Factitious (rare)
Medullary thyroid carcinoma	
Other tumors (10%)	
Islet-cell tumors	
Pheochromocytoma	
Ectopic CRH (<1%)	

ACTH, Adrenocorticotropin; *CRH,* corticotropin-releasing hormone.

frequently 20 to 40 years, whereas ectopic ACTH syndrome has a peak incidence at 40 to 60 years. Therefore, the risk of an extrapituitary tumor is increased in an older patient with Cushing's syndrome. Children with Cushing's syndrome have a higher risk of malignant adrenal tumors.

12. The patient with obesity, hypertension, irregular menses, depression, and hirsutism looks like she may have Cushing's syndrome. What should I do?

There are three widely used screening tests for Cushing's syndrome that have comparable sensitivity and specificity, and each can be used in the initial evaluation of a patient with suspected Cushing's syndrome (Fig. 28.1). Patients with clinical features suspicious for Cushing's syndrome and patients with adrenal masses found on imaging should be screened for Cushing's syndrome. There is no single preferred test, as all three of the tests have sensitivity levels of over 90% but lower specificity levels. Tests may need to be repeated, or a combination of tests may need to be done for definitive diagnosis of Cushing's syndrome.

1. *The overnight low-dose dexamethasone suppression test:* The patient takes 1 mg of dexamethasone at 11 PM and her serum cortisol level is measured at 8 AM the next morning. In healthy subjects who are not stressed, dexamethasone (a potent glucocorticoid that does not cross-react with the cortisol assay) suppresses production of CRH, ACTH, and cortisol. In contrast, patients with endogenous Cushing's syndrome should not suppress cortisol production (serum cortisol remains >1.8 mcg/dL) when given 1 mg of dexamethasone.
2. *Measurement of cortisol in saliva samples collected on two separate evenings between 11 PM and midnight:* Salivary cortisol levels are low in subjects without stress late at night but are high in those with Cushing's syndrome because of loss of the normal diurnal rhythm in cortisol production.
3. *Urine free cortisol (UFC) levels, measured in a 24-hour collection of urine:* UFC is elevated in most patients with Cushing's syndrome, but only a value fourfold above the normal range is diagnostic of Cushing's syndrome, because milder elevations can be seen in stress or illness.

13. The patient had a cortisol level drawn after a 1-mg dose of dexamethasone. The level is 7 mcg/dL. Does she have Cushing's syndrome?

Probably not. Acute or chronic illnesses, depression or other psychiatric disorders, and alcohol use disorders activate the hypothalamic–pituitary–adrenal (HPA) axis because of stress and make the patient resistant to dexamethasone suppression. This is sometimes referred to as "pseudo-Cushing's syndrome." In fact, because true Cushing's syndrome is so rare, a nonsuppressed cortisol level after dexamethasone is more likely to be a false-positive result rather than truly indicating the presence of

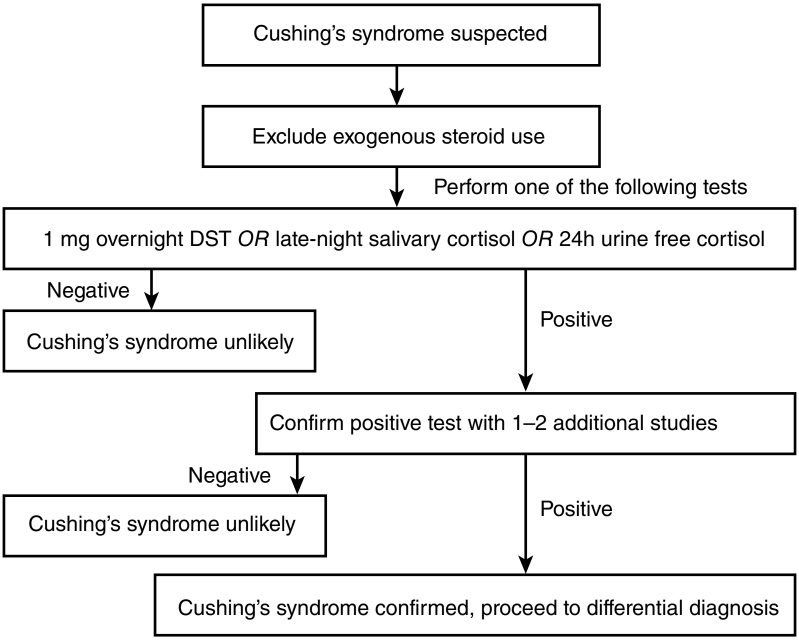
Cushing's syndrome suspected
Exclude exogenous steroid use
Perform one of the following tests
1 mg overnight DST OR late-night salivary cortisol OR 24h urine free cortisol
Negative
Cushing's syndrome unlikely
Positive
Confirm positive test with 1–2 additional studies
Negative
Cushing's syndrome unlikely
Positive
Cushing's syndrome confirmed, proceed to differential diagnosis

Fig. 28.1 Diagnosis of Cushing's syndrome.

Cushing's syndrome. Similar limitations exist for the other two screening tests. Further evaluation is best performed by an endocrinologist and may include performing the alternate screening tests to see if they are concordant, as well as additional biochemical tests (see Fig. 28.1). In some mild or cyclic cases, repeated testing over time is required to definitively diagnose Cushing's syndrome.

14. Further biochemical testing confirms that the patient has Cushing's syndrome. What should I do next?

After you have made the biochemical diagnosis of Cushing's syndrome, the next step is to determine whether she has ACTH-dependent disease or ACTH-independent disease. This distinction is made by measuring morning plasma levels of ACTH. Measurements may need to be repeated a number of times because secretion of ACTH is variable.

15. The patient's ACTH level is "normal." Was the original suspicion of Cushing's syndrome incorrect?

No. A normal or slightly elevated ACTH level is the usual finding in ACTH-secreting pituitary adenomas. More marked elevations of ACTH levels suggest ectopic secretion of ACTH, although small carcinoid tumors also have normal or mildly elevated levels of ACTH. Suppressed ACTH levels (<10 pg/mL), in contrast, suggest a cortisol-producing adrenal tumor. If ACTH levels are indeterminate, measurements of ACTH during stimulation with exogenous CRH can be helpful, although CRH is not available in all countries.

16. After the diagnosis of ACTH-dependent Cushing's syndrome, what is the next step?

Because the most common site of excessive secretion of ACTH is a pituitary tumor (Cushing's disease), radiologic imaging of the pituitary gland is the next step. The best study is high-resolution magnetic resonance imaging (MRI) of the pituitary gland.

17. The pituitary MRI in the patient with ACTH-dependent Cushing's syndrome is normal. Is the next step a search for a carcinoid tumor, under the assumption that the pituitary is not the source of excessive ACTH?

No. At least half of pituitary MRI scans are negative in proven pituitary-dependent Cushing's syndrome because most corticotroph adenomas are tiny and may not be visible on MRI.

18. The pituitary MRI shows a 3-mm hypodense area in the lateral aspect of the pituitary gland. Is it time to call the neurosurgeon?

Again, no. This finding is nonspecific; 10% of healthy adults have pituitary lesions of ≤6 mm that are visible on MRI. It is highly likely that the patient has an ACTH-secreting pituitary tumor, but the MRI does not prove this. The MRI is diagnostic only if it shows a larger tumor (>6 mm or 10 mm, depending on expert opinion).

19. So, what is the next step?

One option is to proceed directly to pituitary surgery because a patient with an abnormal MRI has a 90% chance of having an ACTH-secreting pituitary tumor. To achieve more diagnostic certainty, the gold-standard test is bilateral simultaneous inferior petrosal sinus sampling (IPSS) for ACTH levels. Catheters are advanced through the femoral veins into the inferior petrosal sinuses, which drain the pituitary gland, and blood samples are obtained for ACTH levels. If ACTH levels in the petrosal sinuses are significantly higher than those in peripheral samples, the pituitary gland is the source of excessive ACTH. If there is no gradient between petrosal sinus and peripheral levels of ACTH, the patient probably has a carcinoid tumor somewhere. The accuracy of the test is further increased if ACTH responses to injection of exogenous CRH are measured (although exogenous CRH may not be available in all countries). Bilateral IPSS should be performed by experienced radiologists at referral centers.

20. IPSS shows no gradient in ACTH levels. What is the next step?

Start the search for an ectopic tumor secreting ACTH. In some cases, ectopic ACTH-secreting tumors are obvious, leading to severe clinical manifestations and extremely high cortisol levels that require urgent treatment. However, many ectopic ACTH-secreting tumors are small carcinoid tumors that may not be obvious. Likely locations include the lung, mediastinum, pancreas, GI tract, and thyroid (medullary thyroid cancer). Therefore, computed tomography (CT) of the neck, chest, and abdomen should be ordered.

21. IPSS shows a marked central-to-peripheral gradient in ACTH levels. What should be done next?

Transsphenoidal surgery (TSS) should be scheduled with an experienced neurosurgeon who is well versed in examining the pituitary for small adenomas. Approximately 75% of adults with small pituitary tumors causing Cushing's disease achieve remission with TSS. Remission rates are higher with experienced surgeons, increasing to 80–90% for microadenomas. Even if no tumor is visualized on MRI, comparable high remission rates are achieved in experienced hands. Complications from TSS include hypopituitarism, diabetes insipidus, and CSF leak, but complication rates are low with experienced surgeons. Initial remission rates are lower for macroadenomas (>1 cm), and recurrence rates are significant for all tumor sizes (15–65%). ACTH levels from the right and left petrosal sinuses obtained during the sampling study may tell the neurosurgeon in which side of the pituitary gland the tumor is likely to be found, but this information is not 100% accurate.

22. What if surgery is unsuccessful?

If TSS does not cure a patient with Cushing's disease or if it recurs, repeat TSS may be considered. Additional therapies may also be required because patients with inadequately treated hypercortisolism have increased morbidity and mortality rates. Of the various options after failed surgery, none is ideal. Patients may require repeat pituitary surgery, radiation therapy, medical therapy to block cortisol secretion or action, bilateral adrenalectomy, or a combination of these, and decisions regarding adjuvant therapy must be individualized.

23. What medical treatment options are available for Cushing's syndrome?

Medical therapy for Cushing's syndrome is usually prescribed when surgery has failed, but can also be used preoperatively in patients who are in poor medical condition or instead of surgery in nonoperative candidates. There are three main classes of drugs for the medical treatment of Cushing's syndrome: (1) steroidogenesis inhibitors that block cortisol production from the adrenal gland (ketoconazole, metyrapone, mitotane, etomidate, osilodrostat), (2) pituitary-directed therapies to lower ACTH secretion (cabergoline, pasireotide), and (3) glucocorticoid receptor–directed therapy to block cortisol effects on other organs (mifepristone). There are pros and cons for each drug, including efficacy, adverse effects, costs, availability, induction of adrenal insufficiency, drug–drug interactions, teratogenicity, difficulties with monitoring and dose titration, and decisions regarding combination therapy. These decisions should be made by an experienced endocrinologist.

24. What about radiation therapy for Cushing's disease?

Radiation therapy for Cushing's disease can be used as an adjuvant therapy in cases of persistent or recurrent disease, or in patients who are poor surgical candidates. Stereotactic radiosurgery can be employed to treat small pituitary tumors, while conventional fractionated radiation therapy is used for larger tumors, extrasellar extension, or tumors close to the optic chiasm. Radiation therapy for pituitary-dependent Cushing's syndrome leads to remission rates of 65–80% but takes months to years to be effective, so medical therapy must be used in the meantime. The most common side effect of radiation therapy is hypopituitarism, which is more common with conventional radiation therapy.

25. Why not just take out the patient's adrenal glands?

Bilateral adrenalectomy can be safely performed via a laparoscopic approach, with low morbidity in experienced hands. However, this leads to lifelong adrenal insufficiency and dependence on exogenous glucocorticoids and mineralocorticoids. The other main drawback is the development of Nelson's syndrome in approximately 20% of patients after adrenalectomy. Nelson's syndrome is the appearance, sometimes years after adrenalectomy, of an aggressive corticotroph pituitary tumor. The risk of Nelson's syndrome may be lower in more recent series due to regular MRI monitoring, since Nelson's syndrome tumors usually appear and grow slowly over years. Despite these risks, bilateral adrenalectomy is a viable option for patients who have failed initial surgery, with continued monitoring for the emergence of Nelson's syndrome.

26. What are the correct diagnostic and treatment options for patients with ACTH-independent (adrenal) Cushing's syndrome?

Patients with adrenal Cushing's syndrome should undergo an adrenal CT scan. A mass is usually present, and surgery should be planned. Most cases of adrenal Cushing's syndrome are caused by benign unilateral adrenal adenomas, which should be excised by an experienced adrenal surgeon, in most cases via laparoscopic surgery. If the mass is obviously adrenal cancer, surgery may still help in debulking the tumor and improving the metabolic consequences of hypercortisolemia. If there are multiple adrenal nodules, the patient may have a rare form of Cushing's syndrome (bilateral macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease, Carney's complex) and should be evaluated by an endocrinologist. As a caveat, there is also a high prevalence of incidental, nonfunctioning adrenal adenomas in the general population (up to 5%), and therefore CT findings may not be conclusive.

27. What happens to the HPA axis after a patient undergoes successful removal of an ACTH-secreting pituitary adenoma or a cortisol-secreting adrenal adenoma?

The HPA axis is suppressed, and the patient develops clinical adrenal insufficiency, unless he or she is given gradually decreasing doses of exogenous glucocorticoids until the HPA axis recovers. This usually requires 6 to 12 months or even longer postoperatively. Despite the use of glucocorticoids, many patients suffer from glucocorticoid withdrawal symptoms during this period and must be warned that this is common and expected. In fact, postoperative adrenal insufficiency is a marker of successful surgery.

28. What would be the most likely diagnosis if the original patient had all the signs of Cushing's syndrome but *low* urinary and serum levels of cortisol?

The most likely scenario is that the patient is surreptitiously or accidentally ingesting a glucocorticoid that gives all the findings of glucocorticoid excess but is not measured in the cortisol assay. This can include topical and inhaled steroid preparations if used at sufficient doses and duration of therapy. The patient and family members should be questioned about possible access to medications, and special assays can measure the various synthetic glucocorticoids.

29. Besides treatment of Cushing's syndrome itself, what common comorbidities should be addressed in these patients?

Cushing's syndrome is associated with a number of comorbidities, which are more common with prolonged exposure to excess cortisol levels. The comorbidities usually improve following successful treatment, but they may persist. These include hypertension, atherosclerotic disease, impaired glucose tolerance or diabetes mellitus, thromboembolic events, osteoporosis and fractures, proximal myopathy, glaucoma, psychiatric complications, and cognitive deficits. These should be treated with standard therapies as indicated. Bone densitometry testing is advisable to detect osteopenia or osteoporosis; all patients with Cushing's syndrome should be advised on lifestyle measures for osteoporosis prevention (adequate intake of calcium and vitamin D and regular exercise, as tolerated), and strong consideration should be given to the addition of osteoporosis medications if their fracture risk is sufficiently high.

30. Should prevention of venous thromboembolic events and infectious complications also be a part of the management plan?

Cushing's syndrome is associated with hypercoagulability and a significantly increased risk of venous thromboembolism (VTE) events. The cause appears to be an increase in plasma levels of clotting factors, especially factor VIII and Von Willebrand factor complex and a reduction in plasma fibrinolytic activity. Patients with Cushing's syndrome should be evaluated for their overall VTE risk. Perioperative VTE prophylaxis is recommended in all patients, and if the VTE risk is sufficiently high, chronic prophylaxis may be warranted until the disorder is cured or controlled.

Because of the increased risk of infections resulting from hypercortisolism, it is recommended that clinicians offer age-appropriate vaccinations, especially those for influenza, pneumococcal pneumonia, and herpes zoster, to these patients.

31. Do tumors ever cause Cushing's syndrome by making excessive CRH?

Yes. Occasionally patients who undergo TSS for a presumed corticotroph adenoma have corticotroph hyperplasia instead. At least some of these cases are secondary to ectopic production of CRH from a carcinoid tumor in the lung, abdomen, or other location. Therefore, levels of serum CRH should be measured in patients with Cushing's syndrome and corticotroph hyperplasia. If the levels are elevated, a careful search should be performed for possible ectopic sources of CRH.

KEY POINTS

Cushing's Syndrome

- The clinical manifestations of Cushing's syndrome can be subtle or nonspecific.
- Most patients who look like they might have Cushing's syndrome do not.
- Screening biochemical tests for Cushing's syndrome can be misleading, and repeated testing or more extensive confirmatory testing is often necessary.
- Most patients with Cushing's syndrome have a small pituitary tumor producing adrenocorticotropin.
- Patients with pituitary tumors causing Cushing's syndrome should undergo pituitary surgery by an experienced neurosurgeon because none of the other treatment options are ideal.

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CHAPTER 29

Glycoprotein Secreting Pituitary Tumors*

Jill K. Wagoner

1. What are glycoprotein hormones?

Glycoprotein hormones are thyrotropin (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and chorionic gonadotropin (CG). They are composed of two non-covalently bound subunits: the alpha subunit (α-SU) is similar among all four hormones; in contrast, the beta subunit (β-SU) is unique both immunologically and biologically for each hormone.

2. Name two types of glycoprotein secreting pituitary tumors and secretory products.

Gonadotropinomas: LH, FSH, LHβ, FSHβ, α-SU
Thyrotropinomas (TSH-omas): TSH, α-SU

3. Do pituitary tumors secrete only a single hormone?

No. Many tumors make two or more hormones or subunits. At times, sufficient quantities of multiple hormones are secreted to produce clinical symptoms characteristic of several syndromes within the same patient. At other times no clinical syndrome is apparent.

4. Under what circumstances should a TSH-secreting tumor be considered?

- Suspected hyperthyroidism
- Elevated serum free thyroxine (T_4) or free triiodothyronine (T_3) with detectable or elevated TSH
- Pituitary tumors

5. Describe the differential diagnosis for patients with a transient increase in serum T_4 and detectable or elevated TSH.

Exogenous

- L-Thyroxine (L-T_4) therapy (noncompliant patient who took L-T_4 just before blood was drawn)
- Other drugs (amiodarone, amphetamines, heparin, NSAIDs)

Endogenous (subgroup of nonthyroidal illness)

- Acute psychiatric illness
- Acute liver disease

6. Describe the differential diagnosis for patients with a permanent increase in serum total T_4 and detectable or elevated level of serum TSH.

Binding protein disorders

- Excessive thyroxine-binding globulin (TBG)
- Abnormal thyroxine-binding prealbumin (TBPA) (transthyretin)
- Familial dysalbuminemic hyperthyroxinemia (FDH)
- T_4 or T_3 antibodies (leading to artefactual high thyroid hormone levels in analog assays)
- TSH heterophile antibodies to mouse immunoglobulins (requires separate cause for T_4 elevation)

Inappropriate TSH secretion

- Resistance to thyroid hormone (generalized, central)
- TSH-secreting pituitary adenoma

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*Revised from Previous Chapter that was authored by Majlinda Xhikola, Shon Meek and Robert C. Smallridge

7. What tests aid in the differential diagnosis of the patient with elevated serum total T_4 and detectable or elevated TSH?

The history and physical examination usually rule out medications and nonthyroidal illnesses. The most important laboratory test is the free $T_{4.}$ A normal free T_4 with an elevated total T4 strongly suggests one of the binding protein disorders. An elevated free $T_{4,}$ in contrast, generally narrows the differential to two disorders: a thyroid hormone resistance syndrome or a TSH-secreting pituitary tumor. Clinical thyrotoxicosis is commonly present in patients with either condition but can also be absent in patients with thyroid hormone resistance syndromes. One should confirm the abnormal test results in a second laboratory before initiating a workup for these uncommon disorders.

8. How can one distinguish between the hyperthyroid patient with thyroid hormone resistance or pituitary tumor?

Patients with a TSH-secreting pituitary adenoma will usually show biochemical evidence of hyperthyroidism, including an elevated sex hormone–binding globulin (SHBG) level, a high serum alpha subunit level, an abnormally high alpha subunit to TSH molar ratio, and a lack of TSH response to stimulation by thyrotropin-releasing hormone (TRH) or suppression by triiodothyronine (T_3). Patients with thyroid hormone resistance have normal SHBG levels, alpha subunit levels, and alpha subunit to TSH molar ratios; their TSH levels respond significantly to stimulation by TRH and suppression by T_3 (Table 29.1).

Dynamic testing for the diagnosis of TSH secreting pituitary adenomas is limited due to lack of availability of TRH preparations in the United States and the possible cardiovascular risks of T_3 suppression testing (contraindicated in the elderly or patients with known cardiovascular disease). Genetic testing for mutations of the thyroid hormone receptor (TR) beta subunit is available and is positive in approximately 85% of patients with thyroid hormone resistance syndromes. Genetic testing may be particularly advisable in those with either a microadenoma or no obvious sellar lesion on MRI examination (to rule out thyroid hormone resistance). Dynamic MRI scan, sampling of inferior petrosal sinus blood, or somatostatin receptor scintigraphy (OctreoScan) is also helpful in diagnosing TSH secreting tumors.

9. Describe how to calculate an alpha subunit/TSH molar ratio.

See Table 29.2.

10. Name the treatment of choice for TSH-secreting tumors.

Transsphenoidal pituitary surgery is the treatment of choice and produces remission in up to 50% of patients. Results are somewhat better if surgery is followed by radiation therapy in cases of surgical failure. Because more microadenomas are being identified, results are improving.

11. How effective is radiation as the sole therapy?

Surgery remains the first-choice treatment for TSH-secreting tumors. When surgery is unsuccessful or contraindicated, somatostatin analogs and radiotherapy are effective in controlling hyperthyroidism and tumor growth in the majority of patients. The effects of radiotherapy on TSH secretion and tumor mass are greater within the first years after treatment, whereas pituitary deficiencies may occur several years later.

TABLE 29.1 Distinguishing Features of TSH Producing Pituitary Adenoma and Thyroid Hormone Resistance

	TSH-SECRETING PITUITARY ADENOMA	THYROID HORMONE RESISTANCE
Biochemical evidence of hyperthyroidism	Yes	No
SHBG level	High	Normal
Alpha Subunit level	High	Normal
Alpha Subunit to TSH molar ratio	High	Normal
TSH stimulated by thyrotropin-releasing hormone (TRH)	No	Yes
TSH suppression by triiodothyronine (T_3)	No	Yes

TABLE 29.2 Molar ratio = [α-SU (ng/mL) / TSH (mU /L)] x 10

The following are normal alpha subunit/TSH molar ratios:	
If TSH is normal	Molar ratio < 5.7 in normogonadotrophic individuals Molar ratio < 29.1 in hypergonadotrophic individuals
If TSH is elevated	Molar ratio < 0.7 in normogonadotrophic individuals Molar ratio < 1.0 in hypergonadotrophic individuals
TSH and α-SU values are expressed as mU/L and ng/mL, respectively.	

12. List the medical therapies used for TSH-secreting tumors.

Somatostatin analogs (octreotide or lanreotide) decrease serum TSH levels in more than 90% of cases and normalize free T_4 in 75% of cases; tumor size decreases and vision improves. Dopamine agonists (bromocriptine or cabergoline) have shown limited success in this condition. Dexamethasone reduces TSH secretion, but its side effects exclude long-term use. Antithyroid medications (methimazole or propylthiouracil) and beta-adrenergic receptor antagonists may be used to control hyperthyroidism preoperatively.

13. Summarize the role of thyroid gland ablation in the treatment of TSH-secreting tumors.

Thyroidectomy and ^{131}I therapy should be avoided. They do not control TSH secretion and may enhance pituitary activity and growth; however, two patients who have been followed for 8 and 12 years, respectively, have been reported to have had no tumor growth.

14. Do all patients with an enlarged pituitary gland and an elevated level of serum TSH have TSH-secreting tumors?

No. Patients with long-standing hypothyroidism may develop pituitary hyperplasia and a pseudotumor (Fig. 29.1). The mass can extend into the suprasellar region, causing visual field defects. In contrast to TSH-secreting tumors, serum T_4 is always low in this situation. The reported incidence of pituitary hyperplasia in patients with hypothyroidism varies from 25% to 81%; a high incidence (70%) is reported in patients with TSH levels ≥50 mU/L. Shrinkage of the enlarged gland usually occurs with levothyroxine (LT4) therapy. Hyperplasia of lactotrophs may also occur,

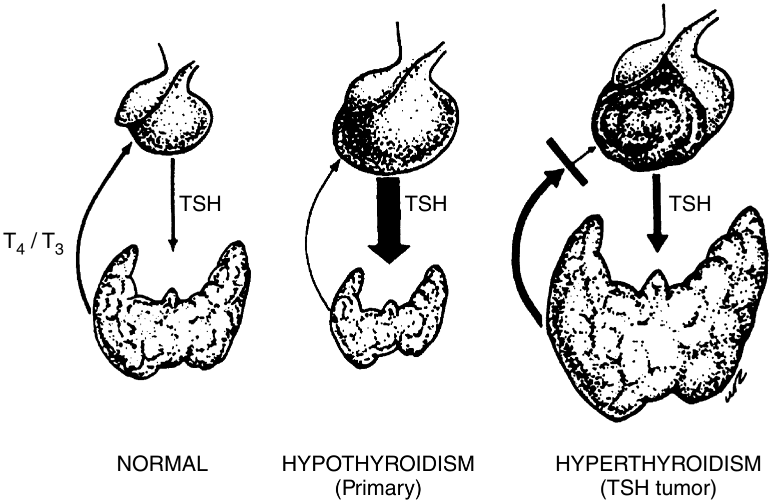

Fig. 29.1 Pituitary–thyroid axis in normal persons and patients with thyrotropin (TSH)-secreting pituitary tumors. On the left is the appropriate feedback loop in euthyroid persons, with the width of the arrows representing the normal serum concentration of TSH and thyroxine (T_4). The middle figure depicts a small thyroid gland due to primary hypothyroidism. The low T_4 levels result in markedly increased secretion of TSH and, in some patients, a generalized hyperplasia of the anterior pituitary gland. On the right is an autonomous pituitary tumor secreting TSH. Serum TSH levels may vary greatly but in all cases are sufficiently biologically active to increase levels of T_4 above normal. The elevated T_4 level has little, if any, ability to suppress tumor function.

TABLE 29.3 Gonadotropinoma Presenting Features

MASS EFFECT (COMMON)	ENDOCRINE EXCESSES (UNCOMMON)
Large tumors with extrasellar growth	Ovarian hyperstimulation
Visual impairment/diplopia	Testicular enlargement
Headaches	Precocious puberty
Apoplexy	
Hypopituitarism	

causing elevated prolactin levels. No patient should undergo pituitary gland surgery without preoperative measurement of both serum T_4 and TSH.

15. What clinical features raise suspicion of a TSH-secreting pseudotumor?

Almost all patients have symptoms of hypothyroidism and the serum T_4 level is always low. The underlying abnormality is usually autoimmune thyroiditis. About 80% of cases of pituitary enlargement with hypothyroidism have occurred in women, whereas only 55% of true TSH tumors were in women. Thyroid antibodies are present in more than 75% of cases with pseudotumor, compared with about 10% of patients with TSH-secreting pituitary tumors that produce hyperthyroidism.

16. Does the presence of abnormal visual fields help distinguish between patients with pituitary hyperplasia due to primary hypothyroidism and TSH-secreting tumors?

No. Abnormal visual fields have been reported in 28% of patients with hypothyroidism-induced pituitary hyperplasia versus 42% with TSH-secreting pituitary tumors. In contrast, patients with thyroid hormone resistance syndromes have normal vision.

17. Does family history provide any clues in distinguishing these disorders?

In pseudotumor from thyrotroph hyperplasia, the family history may be positive for autoimmune diseases (e.g., Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, rheumatoid arthritis, lupus erythematosus, Sjögren's syndrome, vitiligo, Addison's disease, pernicious anemia). In TSH-secreting tumors, a family history of these is usually absent. Most cases of generalized thyroid hormone resistance are familial with autosomal dominant inheritance (e.g., 50% of the family have the abnormality).

18. Which hormones are elevated in the serum of patients with gonadotroph adenomas?

Serum FSH is increased much more often than LH. An increase in α-SU is not specific for gonadotrophs because it may also derive from thyrotrophs. Furthermore, an α-SU/LH (or FSH) molar ratio has not been clinically useful.

19. List the presenting features of patients with gonadotropinomas.

See Table 29.3.

20. When gonadotropin levels are elevated, how can one distinguish a gonadotroph adenoma from primary hypogonadism?

Pituitary gonadotroph adenomas must be considered in the differential diagnosis in reproductive-aged women presenting with the clinical symptom triad of new-onset oligomenorrhea, bilateral cystic adnexal masses (ovarian hyperstimulation), and elevated estradiol and FSH levels with normal or suppressed levels of LH. This distinction can be challenging in postmenopausal women, as they usually have increased levels of LH and FSH. Historically, men with such tumors experienced normal puberty and may have fathered children. On examination, testicular size may be normal or increased due to FSH hypersecretion, and testosterone levels may be elevated due to hypersecretion of intact LH. In contrast, men with hypogonadism may have had abnormal pubertal development or a history of testicular injury and the testes are small.

21. What laboratory tests are helpful?

In primary hypogonadism, both FSH and LH are increased, whereas in patients with gonadotropinomas FSH is elevated but LH is usually normal. When LH is high in men with gonadotropinomas, testosterone is also high rather than low, as in hypogonadism. For unclear reasons, about one-third of patients with a tumor have an anomalous rise in serum FSH or LHβ when given a TRH injection.

TABLE 29.4 Molecular Markers in Pituitary Tumors

	ONCOGENES	TUMOUR SUPPRESSOR GENES
Somatotroph adenoma	CCND1 (Cyclin D1), CREB	
Lactotroph adenoma	FGF4, TGFα	BMP4
Corticotroph adenoma	CCNE1 (Cyclin E), HDAC2	SmarcA4
Thyrotroph adenoma	Pit-1 factor	(TR)-beta gene
Gonadotroph adenoma	STF1, GATA2	RASSF1A
Nonfunctioning adenoma	PRKCA, AKT1, AKT2,	DKC1, MEG3, PLAGL1 (ZAC1)

An MRI scan of the pituitary reveals a large tumor. Occasionally, a patient with long-standing hypogonadism may have some degree of pituitary enlargement due to gonadotroph hyperplasia.

22. How are gonadotropinomas treated?

Pituitary surgery is the treatment of choice. While cure is often impossible, substantial reduction in tumor size and hormone secretion are common. Reduced hormone secretion provides a convenient marker for monitoring tumor recurrence; an abrupt increase in FSH or α-SU should prompt repeat imaging. Radiation therapy is often given after surgery to prevent tumor recurrence.

23. Is medical therapy effective?

Medical therapies have been used in a few cases, but they have not been associated with tumor shrinkage, and their use as a primary therapeutic approach is generally not recommended. Dopamine agonists have reduced FSH levels and improved ovarian hyperstimulation syndrome in a limited number of cases, and it is generally accepted that they are not beneficial in controlling the tumor itself or the clinical syndrome. Somatostatin analogs were used with success in one case of a female patient that led to normalization of estradiol and ovarian volumes but no tumor shrinkage. GnRH agonists have shown limited benefit and also increase the risk of further stimulation of gonadotropin secretion and increase in tumor size. GnRH antagonists (Nal-Glu-GnRH) are used in some cases with inconsistent results.

24. Are pituitary tumors malignant?

Pituitary carcinomas are extremely rare. It is unclear whether they develop as *de novo* carcinomas or as pituitary adenomas that gradually gain malignant features. The majority arise from prolactin- and ACTH-secreting cells and, more rarely, GH-, TSH-, or LH/FSH-secreting cells.

25. What causes pituitary tumors?

The key mechanisms involved in the pituitary tumorigenic process are oncogene activation and tumor suppressor gene inactivation. These can occur either independently or in combination with one another. Selected genes that may be involved in the molecular pathogenesis of pituitary adenomas are included in Table 29.4.

KEY POINTS

Glycoprotein-Secreting Pituitary Tumors

1. Glycoprotein-secreting pituitary tumors include thyrotropin (TSH)-secreting adenomas and gonadotropinomas (luteinizing hormone or follicle-stimulating hormone–secreting tumors).
2. Hyperthyroid patients with detectable serum TSH levels should always be evaluated for inappropriate TSH secretion (either a TSH tumor or thyroid hormone resistance).
3. TSH tumors are managed by transsphenoidal surgery and possibly a somatostatin analog.
4. Hypothyroidism can produce thyrotroph hyperplasia and pituitary pseudotumors.
5. Gonadotropinomas may present with neurologic symptoms due to mass effect and require pituitary surgery.

WEBSITE

Thyroid disease manager. Available at: http://www.thyroidmanager.org

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CHAPTER 30

Water Metabolism

Leonard R. Sanders

1. What is the water composition of the human body?

The water composition of the body depends on age, sex, muscle mass, body habitus, and fat content. Various body tissues have the following water percentages: lungs, heart, and kidneys (80%); skeletal muscle and brain (75%); skin and liver (70%); bone (20%); and adipose tissue (10%). Clearly, people with more muscle than fat have more water. Generally, thin people have less fat and more water. By weight, men's bodies are 60% water, and women's bodies are 50% water. Older people have more fat and less muscle. The average man and woman over 60 years old are made up of 50% and 45% water, respectively (Table 30.1). Most discussions of total body water (TBW) consider a man with 60% body water, weighing 70 kg, and standing 69 inches (175 cm) tall.

2. Where is water located within the body?

Total body water (TBW) comprises water inside the cells (intracellular fluid, ICF) and outside the cells (extracellular fluid, ECF). TBW accounts for 60% of body weight—40% ICF (two-thirds) and 20% ECF (one-third). Of the ECF, interstitial fluid (ISF) makes up approximately three-fourths, and intravascular fluid (IVF) makes up one-fourth. IVF is a major component of total blood volume, necessary to maintain effective vascular pressure. ISF constitutes 15% of body weight, and IVF constitutes 5% of body weight. In a 70-kg man, TBW equals 42 L; ICF water equals 28 L; and ECF water equals 14 L. ISF is 10.5 L, and IVF (plasma) is 3.5 L. Tight regulation of the relatively small volume of IVF maintains blood pressure and prevents symptomatic hypovolemia and congestive heart failure. Normal plasma is 93% water and 7% proteins and lipids. The arterial volume is only 15% of IVF. Although arterial volume is small, its integrity is crucial for maintaining effective circulation and preventing abnormalities of water balance.

3. What is transcellular water (TCW) and its clinical significance?

Transcellular water (TCW) is a distinct component of the extracellular fluid (ECF) formed by cellular transport activities and found in various ducts and spaces throughout the body. Examples include cerebrospinal fluid (CSF) and aqueous humor; secretions in the sweat, salivary, and lacrimal glands; secretions in the pancreas, liver, biliary, gastrointestinal, and respiratory tracts; and peritoneal, pleural, and synovial fluids. Alterations in TCW volume or composition can be associated with various clinical manifestations. Although often overlooked, TCW is vital for physiological function and can contribute to significant clinical complications in disease states. Despite typically constituting a small fraction of body weight (approximately 1.5%), TCW is crucial for transporting secretions to specific sites for enzymatic and lubricant functions. Imbalances in TCW can cause dysfunction. Marked excess of TCW formation—called third spacing—may decrease effective circulating volume (ECV, the volume of blood effectively perfusing tissues), stimulate antidiuretic hormone (ADH) and aldosterone release, increase salt and water retention, and cause edema and hyponatremia. In conditions like severe pancreatitis, burns, and liver disease, extensive third spacing can lead to significant fluid shifts, contributing to hypovolemia and electrolyte imbalances.

4. What is arginine vasopressin (AVP) and its clinical significance?

The nanopeptide arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), plays a crucial role in water retention and blood pressure regulation. AVP is synthesized in the supraoptic (primarily) and the paraventricular nuclei of the hypothalamus as a precursor molecule called preprovasopressin. This precursor undergoes processing, resulting in the formation of prohormone provasopressin. During its transport along axons to the posterior pituitary, provasopressin is cleaved into three components: vasopressin, neurophysin II, and copeptin. After stimulation by increased plasma osmolality or decreased blood volume, vasopressin, which has a half-life of about

TABLE 30.1 Water as a Percent of Body Weight

BODY HABITUS	PERCENTAGE BODY WEIGHT		
	INFANT	MAN	WOMAN
Thin	80	65	55
Medium	70	60	50
Obese	65	55	45

12 minutes, is released into the bloodstream. It then acts on the kidneys to promote water reabsorption, conserving body water and helping maintain blood pressure. Copeptin, with a half-life of approximately 1–2 hours, is a more stable surrogate marker for AVP secretion, making it easier to measure in clinical settings. Additionally, AVP's high concentration in the posterior pituitary, stored in structures known as Herring bodies (neurosecretory granules in the axon terminals), is responsible for the normal bright spot observed on the lateral view of MRI scans of the pituitary.

5. What factors control the distribution of body water?

Osmotic forces primarily govern the distribution of body water. Water tends to move from areas of lower solute concentration (hypotonic) to higher solute concentration (hypertonic) across semipermeable membranes, aiming to achieve equilibrium. Except for specific regions like the ascending loop of Henle (LOH) and the distal nephron, water moves freely across cell membranes in response to these osmotic gradients. Because tonicity is primarily determined by impermeable solutes, such as sodium, alterations in solute concentrations often indicate underlying water metabolism disorders. In addition to water distribution shifts, changes in total body water (TBW), blood volume, and effective circulating volume (ECV) impact overall water balance.

KEY POINTS

Water Metabolism

- Changes in plasma sodium concentration (P_{Na}) usually reflect changes in body water content or distribution. These changes can occur with low, normal, or high total body sodium. Low P_{Na} typically indicates high total body water (TBW), while high P_{Na} typically indicates low TBW.
- Water always moves across cell membranes from lower solute concentration (hypotonic) to higher solute concentration (hypertonic). This water movement, driven by the concentration of effective osmotic solutes in the intracellular and extracellular fluid, is responsible for the neurological symptoms and signs reflected by changes in P_{Na}.
- Hyponatremia may occur with low, normal, or high osmolality, whereas hypernatremia is always associated with hyperosmolality.
- The body's water content is a balance of input and output.
- A complex interplay of factors controls water balance, including thirst, access to water, solute intake, antidiuretic hormone (ADH), cortisol, aldosterone, natriuretic peptides, baroreceptors, ADH receptors, renal water channels (aquaporins), level of kidney function, and drugs.

6. What is effective circulating volume (ECV)?

ECV is the arterial blood volume necessary to effectively perfuse tissues and maintain normal baroreceptor pressure appropriate for a given level of vascular resistance. ECV is also called effective arterial blood volume (EABV). By inducing changes in baroreceptor tone, alterations in ECV significantly impact water balance. Low ECV, caused, for example, by heart failure or cirrhosis, causes renal salt and water retention. In contrast, high ECV, caused by excessive sodium and water intake, causes renal salt and water loss. Depending on the patient's water intake, these ECV changes may produce significant hyponatremia. Maintaining normal ECV preserves circulatory homeostasis.

7. How do baroreceptors regulate effective circulating volume (ECV)?

Baroreceptors are the primary sensors for changes in ECV. Their main role is to maintain normal pressure, rather than volume, at the level of the baroreceptor sensors, located primarily in the

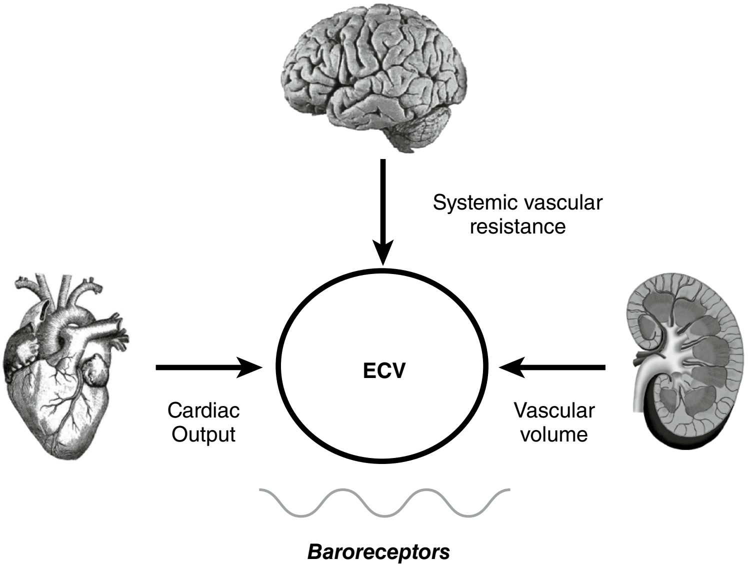

Fig. 30.1 Primary components of the effective circulation (ECV). By stimulating changes in the brain, the heart, and the kidney, baroreceptors have a major impact on vascular pressure and volume and overall water balance. *ECV*, Effective circulating volume.

carotid sinus, aortic arch, atria, pulmonary veins, and afferent renal arterioles. These anatomic locations are critical because perfusion to these areas affects the three main effectors of circulatory homeostasis and ECV: the brain, heart, and kidneys (Fig. 30.1).

8. How does vascular pressure sensed by the baroreceptors relate to ECV and hyponatremia?

Baroreceptors maintain tonic inhibition of vasoconstrictor nerves and natriuretic hormone release while providing tonic stimulation of cardiac vagal nerves. A drop in ECV decreases effective vascular pressure (EVP), baroreceptor tone, tonic inhibition, and tonic stimulation. This results in vasoconstriction, increased heart rate, and increased secretion of renin, aldosterone, angiotensin II, and ADH while decreasing secretion of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and urodilatin. These changes enhance renal Na and water retention. Therefore decreased ECV/EVP predisposes to water retention and hyponatremia. Through atrial stretch receptors, the venous system has similar effects and responds to ECV changes earlier than the arterial system.

9. How does osmolality differ from tonicity, and how do they affect water movement?

Osmolality is the concentration of osmotically active particles of a substance in solution. Tonicity is effective osmolality—the concentration of osmotically active particles restricted to one side of the cell membrane that generates the osmotic pressure responsible for water movement between the ECF and ICF compartments. Effective osmoles are primarily restricted to one side of the cell membrane, contributing to both osmolality and tonicity. They may cause a difference in osmolality between the ECF and ICF (tonicity) and promote water flow. Effective osmoles include Na, glucose, mannitol, sorbitol, glycerol, and glycine. Ineffective osmoles freely cross cell membranes, distribute evenly in TBW, contribute equally to osmolality between the ECF and ICF, and do not change tonicity or water flow. Ineffective osmoles include urea, ethanol, and methanol. Water always moves across cell membranes from lower osmolality to higher osmolality until osmolality on the two sides is equal. The following is always true at equilibrium:

$$\text{ICF osmolality} = \text{ECF osmolality} =$$

10. What formulas are useful in evaluating osmolality and tonicity?

$$\text{ECF osmolality} = 2P_{Na} + \frac{\text{glucose}}{18} + \frac{\text{blood urea nitrogen (BUN)}}{2.8}$$

$$\text{Normal osmolality} = 2(140) + \frac{90}{18} + \frac{14}{2.8} = 280 + 5 + 5 = 290 \text{ mOsm/kg}$$

$$\text{ECF tonicity (effective osmolality)} = 2P_{Na} + \frac{\text{glucose}}{18}$$

$$\text{Normal tonicity} = 2(140) + \frac{90}{18} = 280 + 5 = 285 \text{ mOsm/kg}$$

The normal range for P_{osm} (275–295 mOsm/kg) varies with the normal ranges for P_{Na}, glucose, and urea. The osmolar gap is the difference between measured osmolality (Osm_m) and calculated osmolality (Osm_c). The normal osmolar gap ($Osm_m - Osm_c$) is <10 mOsm/Kg. An increased osmolar gap (>10) indicates that unmeasured osmoles contribute to the measured osmolarity and, if they are effective osmoles, contribute to tonicity. Correction factors for some effective solutes (osmoles) are mannitol/18, sorbitol/18, and glycerol/9. Correction factors for some ineffective solutes (osmoles) are ethanol/4.6 and methanol/3.2.

11. How does P_{Na} relate to TBW, osmolality, and tonicity?

The following formulas are useful for understanding the relationship of P_{Na}, plasma potassium (P_K), total body sodium and potassium $[Na^+ + K^+]$, and TBW. $[Na^+ + K^+]$ estimates total body solute:

$$P_{Na} \cong \frac{\text{total body } [Na^+ + K^+]}{\text{TBW}}$$

$$\text{TBW} \cong \frac{[Na^+ + K^+]}{P_{Na}}$$

$$P_{Na} \cong P_{osm} \cong [\text{total body osmolality}] \cong [\text{total body solutes}] \cong \frac{1}{\text{TBW}}$$

Thus, P_{Na} is proportional to $[Na^+ + K^+]$ and inversely proportional to TBW. An increase or decrease in total plasma Na particles can proportionately change the P_{Na}. However, in clinical medicine, changes in P_{Na} usually reflect changes in plasma water. When P_{Na} is high, plasma water is low. When P_{Na} is low, plasma water is high. Low P_{Na} may occur with low, normal, or high osmolality, whereas high P_{Na} is always associated with hyperosmolality.

12. How does P_K relate to P_{Na} and TBW?

Although 98% of K^+ is intracellular, a K^+ infusion increases P_{Na} by the following mechanisms: In hypokalemia, infused K^+ enters cells. To preserve electroneutrality, Na^+ leaves or chloride (Cl^-) enters cells. ECF water follows K^+ and Cl^- into cells because of increased ICF osmolality. Both mechanisms (Na efflux from cells and water movement into cells) increase the P_{Na}. Patients with hypokalemia infused with equal amounts of potassium chloride (KCl) or sodium chloride (NaCl) have equal increases in P_{Na}. Thus, the addition of KCl to isotonic saline makes hypertonic saline, and infusion of saline with KCl may correct hyponatremia too rapidly (see Questions 36 and 44).

13. What are the input and output levels of water in an average adult?

Total body water (TBW) is a balance of input, including endogenous production and output. In an average adult, daily water input is approximately 1600 mL from liquids, 700 mL from foods, and 200 mL from metabolic oxidation of carbohydrates and fats, totaling about 2500 mL/day. Average daily water losses are 1500 mL via the kidneys, 500 mL via the skin (400 mL from evaporation and 100 mL from perspiration), 300 mL via the lungs (respiration), and 200 mL via the gastrointestinal tract (stool), also totaling about 2500 mL/day. Large water losses can occur with excessive sweating, respiration (exercise), burns, diarrhea, vomiting, and diuresis. Older adults more often have decreased water input due to defects in thirst and altered mental or physical function that prevent access to water and decreased output due to sensitivity to ADH.

14. What are the normal limits of urine output?

Urine output is primarily determined by water intake, the osmotic load from metabolic byproducts, kidney diluting and concentrating ability, and ADH. An average adult on a typical diet needs to excrete 800 to 1000 mOsm of solutes daily. With a normal renal concentrating ability of 50 to 1200 mOsm/kg, the obligate water excretion—the minimum urine volume needed to excrete waste products—can range from 0.8 to 20 L/day. The calculations are as follows:

$$1000\ \text{mOsm/day} \div 1200\ \text{mOsm/L} = 0.8\ \text{L/day at maximal concentration}$$

$$1000\ \text{mOsm/day} \div 50\ \text{mOsm/L} = 20\ \text{L/day at maximal dilution}$$

Higher solute loads, such as from a high-protein diet, require more water excretion. For example, bodybuilders consuming 1400 mOsm of solutes per day may have a urine output of 1.2 to 28 L/day. Conversely, low solute and high water intake can lead to water retention and intoxication, potentially causing hyponatremia and cellular swelling. This can be seen in binge beer drinkers or individuals on a “tea and toast” diet, where urine output may drop to 0.25 to 6 L/day. Therefore urine output varies significantly based on solute load, water intake, kidney function, and ADH, highlighting the kidney and ADH roles in maintaining fluid and electrolyte balance. The extremes of urine output only occur with insufficient ADH action.

15. What are the main factors controlling water metabolism?

The nervous system, baroreceptors, thirst, and hormonal and renal mechanisms are tightly integrated for control of water metabolism (see Fig. 30.1).

16. What are the stimuli of thirst?

Thirst is a conscious desire to drink fluids triggered primarily by:

- Increased plasma osmolality: Osmoreceptors in the organum vasculosum of the anterior hypothalamus sense rising plasma tonicity and stimulate thirst. This osmotic threshold for thirst is approximately 5 mOsm/kg higher than that needed for ADH release.
- Oropharyngeal dryness: Dryness in the mouth and throat stimulates thirst via oropharyngeal receptors. This explains why drinking water quenches thirst quickly, even before changes in plasma osmolality occur.
- Decreased effective circulating volume (ECV): Reduced ECV activates baroreceptors and increases angiotensin II levels, both stimulating thirst.

17. What hormonal mechanisms are involved in the control of body water?

Although natriuretic peptides, renin, aldosterone, angiotensin II, prostaglandins, and neurohumoral changes affect renal water retention and excretion, ADH is the most important hormonal influence. ADH, also called arginine vasopressin (AVP), is secreted by the supraoptic and paraventricular nuclei in the hypothalamus in response to increased osmolality and decreased blood volume. ADH attaches to vasopressin 2 receptors (V2-Rs) on the basolateral membrane of renal collecting tubular cells. This activates cyclic adenosine monophosphate (cAMP) and protein kinase A, causing intracellular water channels called aquaporins (AQPs) to insert into the luminal membrane. Water moves down osmotic gradients from the tubular lumen through AQP channels into the cell and the interstitium.

At least seven AQP isoforms (AQP1–4, AQP6–8) are present in the kidney. AQP1 is constitutively expressed in the proximal tubule and descending LOH and is essential for isotonic fluid reabsorption and water conservation. The collecting duct has high concentrations of AQP2 that serve as the primary target for ADH-mediated water reabsorption. Abnormalities of the V2-R cause most cases of nephrogenic diabetes insipidus (DI), but abnormalities of AQP2 cause some. Increased AQP2 may cause water retention in conditions such as pregnancy and congestive heart failure. Twenty percent of ADH receptors in the collecting tubular cells are vasopressin 1 receptors (V1-Rs). Only at very high levels does ADH activate V1-Rs, which increases prostaglandin E2 and prostacyclin and opposes the antidiuretic effects of excessive ADH.

18. What physiologic changes affect ADH secretion?

ADH, a key hormone in the body's regulatory processes, helps maintain osmotic and volume homeostasis. ADH secretion starts at an osmotic threshold of 280 mOsm/kg and increases proportionately with rises in tonicity. Maximum diuresis occurs at ADH levels <0.5 pmol/L and maximum water reabsorption occurs at ADH levels of 3–4 pmol/Ls. A 1% to 2% increase in plasma osmolality stimulates ADH secretion, whereas an 8% to 10% drop in intravascular volume is required for the same effect. Increased extracellular volume (ECV) raises the osmotic threshold for ADH secretion via baroreceptors, whereas decreased ECV lowers this threshold. Severe volume depletion and hypotension may override the hypoosmotic inhibition of ADH secretion, a phenomenon known as the "law of circulating volume." In such cases, ADH secretion continues despite low osmolality, worsening hyponatremia. This underscores the body's prioritization of maintaining blood volume and pressure over osmolality regulation in critical states.

19. What clinical conditions cause hyponatremia associated with increased ADH secretion or action?

Common clinical conditions that increase ADH secretion include the following.

- SIADH (the syndrome of inappropriate antidiuretic hormone secretion) also called SIAD (syndrome of inappropriate antidiuresis).
- Physiological stimuli: hyperosmolality, hypovolemia, pain, nausea, and stress are potent stimuli for ADH release and are particularly problematic in the postoperative period. They can contribute to life-threatening hyponatremia if hypotonic fluids and ADH-potentiating medications, such as morphine, are administered.
- Endocrine disorders: adrenal insufficiency and moderate to severe hypothyroidism.
- Pregnancy elevates estrogen and progesterone, enhancing the sensitivity of the hypothalamic osmoreceptors. This leads to increased production of ADH and a lower threshold for its release. These two hormones also increase the expression and sensitivity of collecting duct V2 receptors and increase aquaporin-2 (AQP2) water channels. Estrogens also directly increase AQP2. The placenta-produced vasopressinase may counter some of these effects.
- CNS disorders: infections, tumors, and vascular events (thrombosis, hemorrhage).
- Pulmonary disorders: pneumonia, tuberculosis, asthma, atelectasis, cystic fibrosis, positive pressure ventilation, and adult respiratory distress syndrome.
- Ectopic ADH secretion: malignancies, primarily small cell lung cancer, but also cancers of the duodenum, pancreas, ureter, bladder, prostate, and lymphoma.
- HIV infection: multifactorial through associated CNS dysfunction, pulmonary disease, or malignancy.
- COVID-19 infections: direct ADH release with SIADH/SIAD and COVID-19-associated hypothyroidism and adrenal insufficiency.
- Medications: excessive exogenous ADH or desmopressin acetate (DDAVP), oxytocin (in high doses used to induce labor), and other drugs that affect ADH secretion or action (see Table 30.2).

KEY POINTS

Syndromes and Treatment of Water Dysfunction

- Clinical syndromes of water dysfunction include syndrome of inappropriate secretion of antidiuretic hormone, diabetes insipidus, and changes in effective circulating volume (ECV) that can cause marked retention of salt and water, pulmonary and peripheral edema, and severe neurologic dysfunction.
- Effective correction of water problems requires correcting abnormalities of plasma sodium (P_{Na}) and a clear understanding of changes in plasma and urine osmolality (U_{osm}), urine sodium (U_{Na}), urine potassium (U_K), and ECV. Additionally, a thorough assessment of patient volume and neurologic symptoms is essential.
- If neurologic symptoms occur rapidly or are severe, correction of P_{Na} toward normal should be rapid; if symptoms are absent, there is no urgency, and P_{Na} correction should occur more slowly.
- Depending on the water disturbance, treatment includes water restriction or administration; hypertonic, isotonic, or hypotonic saline; sodium; diuretics; antidiuretic hormone; and aquaretics or other medications.

TABLE 30.2 Drugs That Affect Antidiuretic Hormone (ADH) Secretion and Action[a]

Increase ADH Secretion	**Antidepressants** Amitriptyline Protriptyline Desipramine Selective serotonin reuptake inhibitors Duloxetine **Antipsychotics**[a] Fluphenazine Haloperidol Thioridazine Phenothiazines Butyrophenones Monoamine oxidase inhibitors **Other** Ecstasy Nicotine Bromocriptine Carbamazepine Chlorpropamide Clofibrate Cyclophosphamide Ifosfamide Morphine Nicotine Vincristine Angiotensin-converting enzyme inhibitors Amiodarone Methyldopa
Increase ADH Effect	Acetaminophen Carbamazepine Chlorpropamide Cyclophosphamide Nonsteroidal antiinflammatory drugs Tolbutamide
Decrease ADH Secretion	Ethanol Phenytoin
Decrease ADH Effect	Demeclocycline Lithium Acetohexamide Tolazamide Glyburide Methoxyflurane Propoxyphene Colchicine Amphotericin Vinblastine Prostaglandin E2 Prostacyclin

[a] Because psychosis itself may cause the syndrome of inappropriate secretion of ADH (SIADH), one must question the true ADH-stimulatory effect of the antipsychotic drugs. Changes in ADH secretion may be direct or indirect.

20. How does the kidney handle salt and water?

For the kidney to correct excess or deficient water intake, there must be an adequate glomerular filtration rate (GFR) and delivery of filtrate to the LOH and distal nephron. Solute is separated from water in the ascending limb of the LOH, distal convoluted tubule (DCT), and cortical connecting segment; normal ADH action allows controlled water reabsorption in the cortical and medullary collecting ducts. The proximal convoluted tubule reabsorbs 65%, and the descending limb of the LOH absorbs 25% of filtered solute and water isotonically. The ascending limb is impermeable to water but removes solute, resulting in dilution of the luminal filtrate, concentration of the interstitium (important for ADH action), and delivery of 10% of the filtrate to the cortical collecting ducts with an osmolality of 100 mOsm/kg. Without ADH, this fluid (≈ 18 L/day) would be lost in the urine, causing marked dehydration. In the presence of ADH, the collecting duct becomes permeable to water and reabsorbs all but 1% of the filtrate, reducing the final urine volume to only 1.5 to 2.0 L/day. Normal GFR (125 mL/min) means the kidneys filter 180 L of plasma daily and reabsorb 99%. In normal adults, 99% of all Na and water filtered is reabsorbed.

21. What are the causes and consequences of decreased renal water excretion?

The main concerns with reduced water excretion are hyponatremia and associated hypoosmolality. Conditions that impair GFR, delivery of tubular fluid to the distal nephron, the ability of the distal nephron to separate solute from water, or that increase the permeability of the collecting tubule to water all reduce water excretion. These conditions include renal failure, decreased ECV, diuretics (thiazides and loop), and excessive ADH or ADH action.

22. How do hypothyroidism and adrenal insufficiency cause hyponatremia?

Hypothyroidism and adrenal insufficiency reduce cardiac output (stroke volume) and thereby decrease ECV. Hypothyroidism and adrenal insufficiency contribute to hyponatremia by decreasing water excretion and enhancing water reabsorption, as explained below.

Hypothyroidism reduces cardiac output, which decreases ECV and baroreceptor tone and thereby increases ADH secretion. The decreased ECV associated with hypothyroidism also reduces renal blood flow, glomerular filtration, and maximal solute-free water excretion. Failure to maximally dilute urine results from nonosmotic (ECV dependent) ADH release and increased ADH-mediated AQP2 receptors and action.

Adrenal Insufficiency also reduces cardiac output and increases ADH release primarily through altered systemic hemodynamics and loss of negative feedback from low cortisol. Low cortisol also impairs cardiac output and systemic vascular responses to catecholamines, reducing blood pressure and ECV. The resulting drop in vascular filling pressure reduces stretch on arterial baroreceptors, decreasing tonic vagal and glossopharyngeal inhibition of ADH release. These baroreceptor changes override hypoosmotic inhibition of ADH release, increasing ADH secretion. The decreased ECV also lowers GFR, enhancing proximal tubular salt and water reabsorption and reducing filtrate delivery to the distal nephron. Normally, corticotropin releasing hormone (CRH) and ADH are cosecreted from the PVN (paraventricular nuclei) of the hypothalamus. Both hormones work synergistically to release adrenocorticotropic hormone (ACTH) from the anterior pituitary: ADH via the vasopressin V1b receptor and CRH via the CRH-R1 receptor, both located on the pituitary corticotroph. Cortisol provides negative feedback at the hypothalamus and pituitary to inhibit the release of both CRH and ADH. Cortisol deficiency decreases this negative feedback at the PVN, increasing ADH release to enhance water reabsorption.

23. What P_{Na} concentrations are causes for concern?

Although the degree of hyponatremia may be classified by serum sodium level as mild (130–134 mEq/L), moderate (125–129 mEq/L), and severe (<125 mEq/L) or hypernatremia as mild (146–150 mEq/L), moderate (151–160 mEq/L), and severe (>160 mEq/L), the seriousness of hyponatremia or hypernatremia depends on the rapidity of development. Acute changes in P_{Na} (within 48 hours) are always of more concern. Normal P_{Na} ranges from 135 to 145 mEq/L. Patients with a P_{Na} value of 115 or 165 mEq/L may not show any clinical features if the problem develops over several days to weeks. However, both conditions may produce major neurological dysfunction if they develop over hours to days. As a rule, Na concentrations of 125 to 155 mEq/L are not usually associated with symptoms. P_{Na} values outside these limits and occasionally rapidly developing disturbances within these limits may be of major concern. With appropriate care, patients have been reported to survive with P_{Na} as low as 85 mEq/L and as high as 274 mEq/L without permanent sequelae. Although older individuals with chronic P_{Na} levels of 120 to 125 mEq/L may appear asymptomatic, they may have associated gait disturbances and may be at increased risk for falls and fractures. These complications have also been reported with milder hyponatremia (P_{Na} <135 mEq/L). Thus, treatment of this mild hyponatremia may benefit this group.

24. What causes the symptoms and signs of increased or decreased TBW?

The main symptoms and signs of TBW excess (decreased P_{Na}) or TBW deficiency (increased P_{Na}) result from brain swelling and contraction, respectively. If TBW changes occur more rapidly than the brain can adapt, symptoms and signs occur. The severity of the symptoms and signs depends on the degree and rapidity of the TBW change. After adaptation occurs, correcting the disturbance in body water too rapidly may be more deleterious than the initial disturbance.

25. What are the symptoms and signs of hyponatremia and hypernatremia?

The severity of symptoms and signs of hyponatremia or hypernatremia are proportional to the degree and rapidity of changes in P_{Na}.

- *Hyponatremia:* headache, confusion, muscle cramps, weakness, lethargy, apathy, agitation, nausea, vomiting, anorexia, altered levels of consciousness, seizures, depressed deep tendon reflexes, hypothermia, Cheyne-Stokes respiration, respiratory depression, coma, and death.
- *Hypernatremia:* weakness, irritability, lethargy, confusion, somnolence, muscle twitching, seizures, respiratory depression, paralysis, and death.

26. How does the brain adapt to hyponatremia?

Because ICF and ECF osmolalities must always be equal, developing hyponatremia and decreased P_{osm} immediately shift water into the brain, raising intracranial pressure (ICP). Increased ICP causes loss of ICF NaCl into CSF. Over the next several hours, there is also loss of intracellular K^+ and, over the next few days, loss of organic solute. These changes lower ICF osmolality and return the brain volume toward normal. However, if severe hyponatremia occurs too rapidly, there is not enough time for cerebral adaptation. Brain edema occurs, further increasing ICP; the brain may herniate, and the patient may die.

27. How does the brain adapt to hypernatremia?

With acute hypernatremia and increased P_{osm}, water immediately shifts out of the brain and decreases ICP. Decreased ICP promotes movement of NaCl from the CSF into the brain ICF, partially correcting the volume loss. Within hours, further brain adaptation occurs, increasing brain ICF K^+, Na^+, and Cl^-. The resulting increase in osmolality pulls water from the ECF and restores about 60% of the brain volume. Over the next several days, the brain accumulates organic solutes (osmolytes), previously called *idiogenic osmoles*, which return the brain volume to a near-normal level. These solutes include glutamine, taurine, glutamate, myoinositol, and phosphocreatine. If the brain has no time to adapt to rapidly developing hypernatremia, it shrinks, retracts from the dura, and tears vessels, causing intracranial hemorrhage, increased ICP, compressive injury, herniation, and death.

28. How should you approach the patient with hyponatremia?

Hyponatremia occurs in 1% of outpatients, >4% to 15% of hospitalized patients, 18% of elderly nursing home residents, and nearly 30% of intensive care unit (ICU) patients. For the evaluation of hyponatremia, first clinically assess the patient's volume status—whether hypovolemic, euvolemic, or hypervolemic. Begin with a history and physical examination. Inquire about diuretics, cathartics, other medications (see Table 30.2), diarrhea, excessive urination, nausea, vomiting, diabetes, kidney disease, and liver disease. Ask about dizziness or loss of balance. Because total body volume is proportional to total body Na, a thorough assessment of the patient's volume status helps determine ECV and therapy. Patients whose neck veins are flat while they are supine and who have postural changes in blood pressure (BP) and pulse (standing BP decreases by >20/10 mm Hg and pulse increases by >20 beats/min) are hypovolemic, and invariably saline (NaCl and water) depleted. Patients with distended neck veins and edema are hypervolemic and have salt and water (saline) excess. Patients with hyponatremia with no postural changes and no edema are clinically euvolemic, but volume may be subclinically increased or decreased. After the history and physical, assess the acuity and severity of symptoms. Hyponatremia (P_{Na} <135 mEq/L) may be classified as mild (>129 mEq/L), moderate (125–129 mEq/L), and severe (<125 mEq/L). The treatment depends on symptoms, and if symptoms are severe, the hyponatremia requires immediate treatment before extensive assessment (see Question 25). To evaluate the patient further, consider if the hyponatremia is hypertonic, isotonic, or hypotonic by measuring the P_{osm}. Also, measure the U_{osm} and the osmolar gap. If P_{osm} is elevated (hypertonic hyponatremia with P_{osm}

TABLE 30.3 Causes of Hyponatremia[a]

PATHOPHYSIOLOGY	ASSOCIATED CONDITIONS
Renal saline loss and decreased ECV urine sodium (U_{Na}) >30 mEq/L	Diuretics Osmotic diuresis (glucose, urea, mannitol) Primary adrenal insufficiency Renal tubular acidosis ($NaHCO_3$ loss) Salt-losing nephritis Ketonuria Cerebral salt wasting
Nonrenal saline loss and decreased ECV U_{Na} <30 mEq/L	Vomiting Diarrhea Pancreatitis, rhabdomyolysis, burns Peritonitis, bowel obstruction
Water excess U_{Na} >30 mEq/L	SIADH Drugs (see Table 30.2) Secondary adrenal insufficiency Hypothyroidism
Sodium (Na) and water excess with decreased ECV U_{Na} <30 mEq/L	Congestive heart failure Cirrhosis Nephrotic syndrome
Na and water excess with increased ECV U_{Na} >30 mEq/L	Acute renal failure Chronic renal failure Pregnancy

[a] Hyponatremia always means too much plasma water relative to Na. Thorough volume assessment is crucial. Volume loss (renal or nonrenal) usually means saline (salt >water) loss and is associated with decreased ECV. Volume excess (hypervolemic) usually means saline (water >salt) excess with associated edema and may be associated with decreased or increased ECV. Water excess usually causes mild excess of volume that affects baroreceptor activity. U_{Na} reflects renal perfusion, tubular integrity, and hormonal status. When U_{Na} >20–30 mEq/L, the kidney contributes to Na loss; and when U_{Na} <20–30 mEq/L, the kidney is conserving Na. ECV, Effective circulating volume; SIADH, syndrome of inappropriate antidiuretic hormone.

>295 mOsm/kg) and the osmolar gap is normal (<10 mOsm/kg), the cause is usually obvious – very high glucose or BUN. If P_{osm} is elevated (hypertonic hyponatremia with P_{osm} >295 mOsm/kg) with a high osmolar gap (>10 mOsm/kg), ECF is high in osmotically active substances other than sodium, glucose, and urea, such as mannitol, maltose, and glycine. The patient may have a recent history of treatment for increased ICP, recent prostate or uterine surgery, or intravenous immunoglobulin (IVIG) administration. When P_{osm} is normal (isotonic hyponatremia with P_{osm} 280–295 mOsm/kg) with a high osmolar gap, there may be displacement of water in the assay volume by excess lipid (hypertriglyceridemia) or protein (multiple myeloma), causing pseudohyponatremia. With pseudohyponatremia, the measured P_{osm} is normal, and the osmolar gap is increased to >10 mOsm/kg. Measurement of P_{Na} without dilution with a direct Na-selective electrode gives a true P_{Na} concentration that is normal. Last, when P_{osm} is low (hypotonic hyponatremia with P_{osm} <280 mOsm/kg), the P_{osm} is considered appropriate for the P_{Na}, and the osmolar gap is usually normal. Measuring U_{osm} is helpful in the differential diagnosis. If U_{osm} <100 mOsm/kg consider primary polydipsia, beer potomania, a tea-and-toast diet, or malnutrition (see Questions 45 and 48). However, most patients with hypotonic hyponatremia have a U_{osm} >100 mOsm/kg (>200 mOsm/Kg in advanced chronic kidney disease [CKD]). This is compatible with a diluting defect and an ADH effect (appropriate or not). Here, the initial assessment of volume status is important to direct treatment to correct the underlying disorder, as outlined in Tables 30.3 and 30.4. Measurement of urine sodium is critical to diagnosis and treatment as well. U_{Na} <30 mEq/L suggests decreased ECV and U_{Na} ≥30 mEq/L suggests normal or increased ECV. If patients have lost saline, give them saline. If they have retained too much water, restrict their water. If they have retained too much salt and water but more water than salt, restrict their salt and water, with water restricted more than salt. It sounds simple. However, sometimes it is difficult to determine the subtle changes in volume status that are key to this assessment (see Question 29). Carefully use loop diuretics in patients with hypervolemia and 3% saline in acutely symptomatic patients (see Question 47).

TABLE 30.4 Approach to Hyponatremia[a]

CONDITION	POSTURAL SIGNS	EDEMA	U_{NA} (MEQ/L)	TREATMENT
Renal Sodium (Na) loss	Yes	No	>30	Isotonic saline
Nonrenal Na loss	Yes	No	<30	Isotonic saline
H_20 excess	No	No	>30	Restrict water
Na + H_20 excess	No	Yes	<30	Restrict water > salt
Na + H_20 excess	No	Yes	>30	Restrict water > salt

[a] Marked hyperlipidemia or hyperproteinemia causes pseudohyponatremia and artifactually lowers the standard measurement for plasma sodium (P_{Na}). Measuring P_{Na} undiluted with direct Na-selective electrodes corrects for the excess lipid and protein and provides a true P_{Na} reading. However, routine measurement or prior dilution give falsely low results for the P_{Na}. Measuring Posm helps differentiate pseudohyponatremia. Osmometer-measured plasma osmolality (P_{osm}) measures only the osmotic activity of plasma water that excludes lipids and proteins. Measured P_{osm} is normal in pseudohyponatremia, and the osmolar gap is increased to >10 mOsm/kg because of artifactually low measured P_{Na}. Use loop diuretics carefully to treat edema and 3% saline for symptomatic acute hyponatremia.

29. What is the importance of an initial thorough volume assessment in patients with hyponatremia?

A thorough volume assessment is essential to help determine the underlying cause of hyponatremia (see Table 30.3) and to guide treatment (see Table 30.4). The volume status is best assessed by looking at neck veins, orthostatic vital signs, and edema. At times, even the best clinician cannot make a good evaluation of ECV, but central venous catheterization is rarely necessary. U_{Na} and edema are other valuable ECV clues. Body weight should be measured daily, and orthostatic vital signs should be assessed serially as necessary. Initial laboratory tests should include P_{osm}, general blood chemistry panel (Na, K, Cl, carbon dioxide [CO_2], creatinine [Cr], blood urea nitrogen [BUN], glucose, albumin, calcium [Ca], Mg); U_{Na}, U_{Cl}, U_{Cr}, U_{osm}; and fractional excretion of Na. The presence or absence of edema and the U_{Na} value are most helpful.

30. How should you characterize and diagnose the patient with SIADH?

SIADH, which has also been called SIAD or *syndrome of inappropriate antidiuresis*, occurs when there is evidence of continued secretion of ADH in the absence of an appropriate osmotic or volume stimulus. Clinical euvolemia, hypotonic plasma, and less than maximally dilute urine are the clues to SIADH. The patient should be approached as discussed in Question 28. It is important to establish normovolemia by physical examination. Then, P_{osm}, U_{osm}, P_{Na}, U_{Na}, and U_K should be ordered. Finally, pituitary, adrenal, and thyroid dysfunction must be excluded before a diagnosis of SIADH can be made. Confirmatory criteria of SIADH include low P_{Na} (<135 mEq/L), low P_{osm} (<280 mOsm/kg), U_{osm} >100 mOsm/kg, U_{Na} >30 mEq/L, and $[U_{Na} + U_K] > P_{Na}$. Patients with SIADH are usually said to have normal volume status. However, they, in fact, have excess TBW. Unlike excess saline, which is limited to ECF, excess water distributes two-thirds to the ICF and one-third to the ECF (see Fig. 30.2). Thus, ECF excess is minor and not usually perceptible by clinical examination. Nonetheless, patients with SIADH have mildly increased ECV, which is sensed by the kidneys. The GFR is increased, causing low serum levels of uric acid (<4 mg/dL), BUN, and creatinine. The increased ECV also increases secretion of ANP, which, along with the increased GFR, promotes natriuresis. These are the classic findings in SIADH. SIADH does not protect against dehydration and other conditions that can obscure the classic presentation. For example, a patient with ectopic ADH from lung cancer may present with dehydration from diarrhea, lack of food intake (solute), and lack of water intake from debilitation. In this instance, the U_{Na} and U_{Cl} may be <20 mEq/L. In complex cases, directly measuring ADH or copeptin, a more stable surrogate of ADH secretion, can be helpful in diagnosing SIADH.

31. How do you treat the patient with SIADH?

SIADH should be treated initially with water restriction (500–1000 mL/day). However, the fluid restriction needed to correct hyponatremia is often not tolerated, especially when $[U_{Na} + U_K]$ is significantly $> P_{Na}$. The combination of a high-sodium (4–8 g/day) diet, high-protein (≥2 g/kg/day) diet, a loop diuretic (e.g., furosemide 20 mg twice daily), and water restriction may be more practical. If water restriction and dietary modification are not tolerated or are insufficient, oral

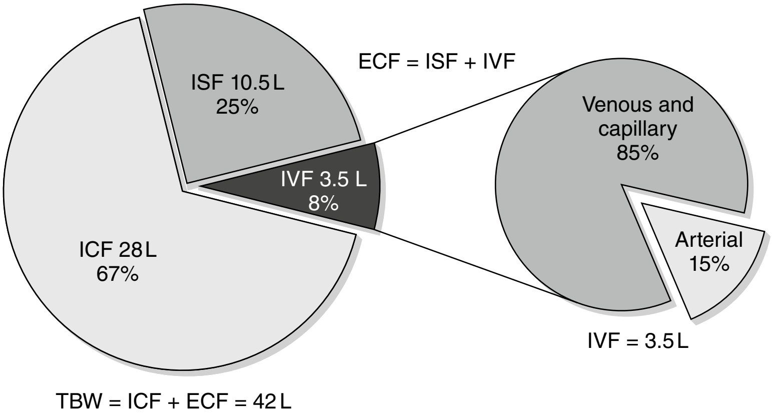

Fig. 30.2 *Left*, Distribution of body water; *right*, total blood volume. *ECF*, Extracellular fluid; *ICF*, intracellular fluid; *ISF*, interstitial fluid; *IVF*, intravascular fluid; *TBW*, total body water.

urea 15 to 60 g/day may help correct the hyponatremia by increasing the osmotic excretion of free water and decreasing natriuresis. Similarly, the use of an SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin) can increase free water clearance and raise serum sodium levels. Demeclocycline and lithium carbonate both act on the collecting tubule to diminish the response to ADH and improve hyponatremia. However, because of potential toxicities, both medications are usually avoided unless there are no other options for treatment. Demeclocycline and lithium carbonate are dosed orally at 600 to 1200 mg/day in two to four divided doses. Because lithium carbonate can cause neurologic, cardiovascular, and other toxicities, it should be avoided unless there are no other therapeutic options. Both drugs may cause nephrotoxicity, and demeclocycline may cause severe renal failure in patients with cirrhosis. Thus, demeclocycline is contraindicated in patients with cirrhosis and severe liver disease, and lithium should be avoided if the GFR is <30 mL/min per 1.73 m2. V2-R antagonists (vaptans) given orally (tolvaptan) or intravenously (conivaptan) have also proven useful for short-term SIADH treatment (see Question 42). Although careful monitoring of P_{Na} is important and the expense of these aquaretics may be prohibitive, these V2-R antagonists may be needed to treat hyponatremia when other interventions fail. Because of the slow response time for change in P_{Na} (days), vaptans are not indicated for the treatment of neurologic symptoms related to acute hyponatremia. They are also contraindicated in severe liver disease and are not indicated for chronic therapy (>30 days). When possible, it is important to correct the underlying abnormality or contributory causes of the SIADH (see Questions 18 and 19). The treatment of markedly symptomatic hyponatremia is discussed in Question 40.

32. What are the five patterns of ADH secretion in SIADH?

Four classic SIADH patterns are distinguished according to the ADH responses to Posm, and one additional pattern, Type E, was more recently described.

- Type A (unregulated ADH secretion): ADH secretion is erratic and unpredictable, with no clear relationship to plasma osmolality. ADH levels are often high. This pattern is typically seen in ectopic ADH production from tumors like small-cell lung cancer.
- Type B (reset osmostat): ADH secretion maintains a normal relationship with plasma osmolality, but the threshold for ADH release is lower than normal (e.g., 260–275 mOsm/kg or plasma sodium concentration of 125–135 mEq/L). This pattern is common in pregnancy.
- Type C (ADH leak): There is a continuous, low-level secretion of ADH within the physiologic range. ADH levels do not suppress with low plasma osmolality or increase with high plasma osmolality, suggesting a loss of normal feedback control. This pattern is more often seen with pulmonary infections like pneumonia.
- Type D (nephrogenic syndrome of inappropriate antidiuresis): This type is characterized by normal osmoregulation of ADH secretion. However, the kidneys fail to dilute the urine effectively in response to ADH, leading to concentrated urine even when ADH levels are appropriately suppressed.

- Type E: In this type, ADH levels decrease as plasma sodium concentration increases during hypertonic saline infusion. This paradoxical response is likely caused by dysfunctional baroreceptor signaling despite normovolemia.

33. What are the main causes of polyuria?

Polyuria is a urine output >3.0 L/day or 30 ml/kg. Four main disorders cause polyuria: (1) central neurogenic diabetes insipidus (DI) (defect in ADH secretion)—also termed *AVP deficiency*, (2) nephrogenic DI (defect in ADH action on the kidney) —also called AVP resistance, (3) psychogenic polydipsia (psychosis), and (4) dipsogenic DI (defect in thirst center). All forms of DI may be partial or complete. In general, patients with DI have $U_{osm} < P_{osm}$, and often the U_{osm} is <100 mOsm/kg. Polyuria also may occur from osmotic diuresis in such conditions as diabetes mellitus (glucose), recovery from renal failure (urea), and intravenous (IV) infusions (saline, mannitol). In the latter cases, the diagnosis is usually clear from the history and U_{osm} is $>P_{osm}$. See Table 30.2 for drugs and conditions that decrease ADH secretion and action. Causes of acquired nephrogenic DI include chronic renal disease, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypercalcemia), drugs (lithium, demeclocycline, cisplatinum), sickle cell disease (damaged medullary interstitium), diet (increased water and decreased solute—beer, starvation), and inflammatory or infiltrative renal diseases (multiple myeloma, amyloidosis, sarcoidosis). DI may also be associated with specific genetic abnormalities. Hereditary central DI is usually autosomal dominant and manifests in childhood rather than at birth. Wolfram's syndrome results from a familial defect on the short arm of chromosome 4 and has associated central DI, diabetes mellitus, optic atrophy, and deafness (DIDMOAD). Congenital nephrogenic DI results from abnormalities of the V2-R or AQP2 channels; in these conditions, symptoms of polyuria and dehydration appear in the first week of life. Most cases of congenital nephrogenic DI (90%) are related to abnormalities of the V2-R and are X-linked; therefore they are almost always limited to expression in males. Greater than 150 mutations have been noted to cause DI related to V2-R abnormalities. Nephrogenic DI related to abnormalities of AQP2 (10%) may be autosomal dominant or recessive. When recessive and in a female, the DI is likely caused by a mutation on chromosome 12.

34. How do you distinguish patients with polyuria and the various forms of DI from patients with excessive water drinking?

P_{Na}, BUN, and uric acid are all relatively low in excessive water drinking. In DI, P_{Na} and uric acid are relatively high, and BUN is relatively low. Central DI, also called AVP deficiency (AVP-D), often has an abrupt onset resulting from the loss of a critical amount of ADH caused by destruction of >80% to 90% of the ADH-secreting hypothalamic neurons. Patients with central DI also prefer ice-cold water. The cause of polyuria is often clear from the history and basic laboratory values. A water restriction test (WRT) can be performed if the diagnosis is in doubt. Other names for the WRT are the *dehydration test* and the *water deprivation test*. The test may take 6 to 18 hours, depending on the initial state of hydration. The WRT should not be performed in patients with hypovolemia, hypothyroidism, adrenal insufficiency, uncontrolled diabetes mellitus, or renal insufficiency. As outlined in Question 35, the WRT is difficult and time-consuming to perform. Copeptin measurement may help define polyuria syndromes like AVP-D more easily; measuring copeptin at baseline and after a 3% saline infusion has been used to differentiate causes of polyuria and DI. Copeptin is a stable surrogate marker of vasopressin secretion. Without prior water deprivation, a single baseline copeptin level >21.4 pmol/L was found to differentiate AVP-D from other etiologies with 100% sensitivity and specificity, and a post-3% saline-stimulated copeptin >4.9 pmol/L differentiated primary polydipsia from partial central DI with 94% sensitivity and specificity, rendering water deprivation testing and desmopressin administration unnecessary. However, studies with copeptin are preliminary, and reliable commercial copeptin assays are hard to find. For now, the diagnostic "gold standard" test to differentiate polyuria and polydipsia syndromes is still the WRT.

35. How is the WRT performed?

- Office testing is acceptable unless the patient cannot be watched closely, in which case hospitalization may be required.
- Measure baseline weight, P_{osm}, P_{Na}, PBUN, plasma glucose, urine volume, U_{osm}, U_{Na}, and U_K. During the test, measure hourly weight, urine volume, and U_{osm}.

- Allow no food or water.
- Watch the patient closely for signs of dehydration (hypotension, tachycardia) and surreptitious water drinking.
- End the WRT when U_{osm} has not increased by >30 mOsm/kg for 3 consecutive hours, P_{osm} has reached 295 to 300 mOsm/kg, the patient has lost 3% to 5% of body weight, or hypotension has developed. If weight loss exceeds 3% to 5% of body weight, further dehydration is unsafe.
- At P_{osm} of 295 to 300 mOsm/kg, endogenous ADH levels should be ≥5 pg/mL, and the kidneys should respond with maximal urinary concentration.
- Repeat all baseline measurements toward and at the end of the WRT.
- Give 5 units of aqueous AVP or 2 mcg of desmopressin (DDAVP) subcutaneously.
- Repeat the baseline tests at 30, 60, and 120 minutes.
- Calculate the U_{osm}/P_{osm} and $[U_{Na} + U_K]/P_{Na}$ ratios as a check on measured U_{osm}/P_{osm}.

36. How do you interpret the results of the WRT?

Table 30.5 summarizes the expected results of the WRT. The WRT stimulates maximal endogenous ADH release by increasing P_{osm} and evaluates the kidneys' concentrating ability by measuring U_{osm}. Giving exogenous ADH allows for evaluating the renal concentrating response to ADH if dehydration-induced ADH production is impaired. Baseline and end-test plasma samples should be saved and frozen for later ADH measurement in case the WRT results are equivocal. Expected normal values for PADH are <0.5 pg/mL for P_{osm} <280 mOsm/kg, and >5 pg/mL for P_{osm} >295 mOsm/kg.

37. What are the expected plasma ADH concentrations and urinary osmolality in patients with polyuria after water restriction?

See Table 30.6.

38. How should you evaluate the patient with hypernatremia?

Hypernatremia is uncommon in comparison with hyponatremia, occurring in <1% of hospitalized patients. Indeed, unless patients have an abnormality of thirst or do not have access to water, they usually maintain near-normal P_{Na} by drinking water in proportion to water loss. However, as many as 5% to 10% of ICU patients may have some degree of hypernatremia. Water loss is the usual cause of hypernatremia, and almost all patients require water for treatment (Table 30.7). As discussed in Questions 28 and 29, the patient's volume status must be assessed carefully, including evaluation of skin turgor, mucous membranes, orthostatic vital signs, and jugular venous pressure. After obtaining laboratory results, the patient should be approached as outlined in Table 30.8. Include the approach described in Questions 33 and 34 if the patient has polyuria.

TABLE 30.5 Values Before and After Water Restriction[a]

	BEFORE RESTRICTION		AFTER RESTRICTION		
	P_{osm}	P_{Na}	U_{osm}/P_{osm}	U_{osm}/P_{osm} + ADH[b]	PADH
Normals	Nl	Nl	>1	>1 (<10%)	↑
Psychogenic polydipsia/dipsogenic DI	↓	↓	>1	>1 (<10%)	↑ or Nl
Complete central DI	↑	↑↑	<1	>1 (>50%)	—
Partial central DI	↑	↑	>1	>1 (10–50%)	↓
Complete nephrogenic DI	↑	↑	<1	<1 (<10%)	↑↑
Partial nephrogenic DI	↑	↑	>1	>1 (<10%)	↑↑

[a] Recall that when $U_{osm} > P_{osm}$, there is antidiuresis, and the kidney is retaining free water. The same is true when $[U_{Na} + U_K] > P_{Na}$, and these measurements are more easily obtainable. When $U_{osm} < P_{osm}$ or $[U_{Na} + U_K] < P_{Na}$, there is a net loss of free water with little net clinical ADH effect.

[b] The values in parentheses indicate the percentage changes in U_{osm} (not the U_{osm}/P_{osm} ratios) after 5 units of subcutaneous aqueous vasopressin or 2 µg of desmopressin acetate.

↓, Low-to-normal; ↑↑, high; ↑, high-to-normal; —, undetectable; *ADH*, antidiuretic hormone; *DI*, diabetes insipidus; *NL*, normal.

TABLE 30.6 Expected Values for ADH and U_{osm} After Water Restriction

CAUSE OF POLYURIA	ADH (PG/ML)	U_{OSM} (MOSM/KG)
Normal	>2	>800
Primary polydipsia	<5	>500
Complete central DI	Undetectable	<300
Partial central DI	<1.5	300–800
Nephrogenic DI	>5	300–500

ADH, Antidiuretic hormone; *DI*, diabetes insipidus; U_{osm}, urine osmolality.

TABLE 30.7 Causes of Hypernatremia[a]

PATHOPHYSIOLOGY	ASSOCIATED CONDITION
Renal H_2O loss > Na loss, U_{Na} > 20 mEq/L	Osmotic diuretics Loop diuretics Renal disease Postobstructive diuresis
Nonrenal H_2O loss > Na loss, U_{Na} < 20 mEq/L	Osmotic diarrhea Vomiting Sweating Diarrhea Burns
Excess Na > H_2O, U_{Na} > 20 mEq/L	Cushing's syndrome Primary hyperaldosteronism Excessive intake of sodium chloride (NaCl) or sodium bicarbonate ($NaHCO_3$) Hypertonic saline and bicarbonate Hypertonic dialysis
Renal H_2O loss, U_{Na} > 20 mEq/L	Central diabetes insipidus Nephrogenic diabetes insipidus
Nonrenal H_2O loss U_{Na} < 20 mEq/L	Increased sensible loss No access to water

[a] Hypernatremia always means too little plasma water relative to sodium (Na). With access to water, hypernatremia usually does not occur or is mild. However, unattended patients who are too old, too young, or too sick may not have adequate access to water, and hypernatremia may be severe. Thorough volume assessment is crucial. Volume loss (hypovolemic) usually means renal or nonrenal saline (water > salt) loss and is usually treated with 0.9% to 0.45% saline to correct the volume deficit, followed by water. Volume excess (hypervolemic) usually means saline (salt > water) excess with high total body Na and is treated with water and restriction of salt. A loop diuretic may also be necessary to treat volume overload. Euvolemic hypernatremia results from water loss and is treated with free water replacement, and vasopressin is used if water loss is caused by diabetes insipidus.

TABLE 30.8 Approach to Hypernatremia

CONDITION	POSTURAL SIGNS	EDEMA	U_{NA} (MEQ/L)	U_{OSM}	TREATMENT
Renal H_2O > Na loss	Yes	No	>20	↓–	0.9–0.45% saline
Nonrenal H_2O > Na loss	Yes	No	<20	↑	0.9–0.45% saline
Na excess	No	Yes/No	>20	↑–	Free water/diuretics
Renal H_2O loss	No	No	>20	↓↑–	Free water
Nonrenal H_2O loss	No	No	<20	↑	Free water

Free water = 5% dextrose in water infusion or water orally. Infuse saline to restore the volume deficit when patients show signs of severe volume depletion, such as hypotension or postural changes in blood pressure and pulse. This is appropriate when isotonic (0.9%) saline with an osmolality of 308 mOsm/kg is lower than plasma osmolality. This corrects both the volume deficit and the hypernatremia. After the volume deficit has improved, switch to 0.45% saline and eventually 5% dextrose in water. Loop diuretics are used to treat Na excess.

↑, Hypertonic; ↓, hypotonic; –, isosmotic.

39. How should you diagnose and manage the patient with AVP-D (DI)?

Patients with DI have excessive renal water loss resulting from decreased ADH secretion (central DI or AVP-D) or renal unresponsiveness to ADH, which is also called AVP resistance (AVP-R) or nephrogenic DI. The hallmark of DI is polyuria with hypotonic urine. Mild hypernatremia, low BUN, and relatively high uric acid suggest DI. ADH and oxytocin neurosecretory vesicles are responsible for the normal finding of a high-signal-intensity posterior pituitary lobe that appears as a bright spot on T1-weighted noncontrast (sagittal view) magnetic resonance imaging (MRI). The normal posterior pituitary bright spot is absent in patients with idiopathic central DI. However, the presence of the posterior pituitary bright spot also decreases with age and may be absent in >50% of elderly patients without DI. Abrupt onset of polyuria is also suggestive of central DI. Little ADH is necessary for urinary concentration, and 80% to 90% of the ADH-secreting neurons must be lost before polyuria develops. As described in Questions 33 and 34, DI must first be distinguished from primary polydipsia and identified as central or nephrogenic. Water should be given to prevent dehydration until further evaluation suggests definitive therapy. Mild cases of DI require no treatment other than adequate fluid intake. A patient with DI will probably self-treat with water unless there is a thirst deficit or no access to water. Central DI is treated with DDAVP as a nasal spray or oral tablet. DDAVP is available for oral use (0.1 mg or 0.2 mg tablets) with a starting dose of 0.05 mg once or twice daily and increasing to a maximum of 0.4 mg every 8 hours as necessary. The tablet is only 5% absorbed, and absorption decreases as much as 50% with meals. At least one dose should be given at bedtime. Oral DDAVP is preferred if sinusitis develops from the use of nasal preparations. DDAVP nasal spray (100 mcg/mL solution) is given every 12 to 24 hours, as needed, for thirst and polyuria. It may be administered nasally through a metered-dose inhaler (0.1 mL/spray) or a plastic calibrated tube. The starting dosage is 0.05 to 0.1 mL once or twice daily and titrated up to acceptable urine output. Parenteral DDAVP (4 mcg/mL) may be given intravenously, intramuscularly, or subcutaneously at 1 to 2 mcg every 12 to 24 hours to hospitalized patients. Nephrogenic DI may be partial or incomplete and, therefore, may respond to DDAVP. If possible, the underlying cause should be corrected or ameliorated (see Question 33).

A low-sodium and low-protein diet that does not compromise nutritional needs should be recommended. Regular voiding should be emphasized to avoid overdistending the bladder and prevent bladder dysfunction. Both central DI and nephrogenic DI respond partially to hydrochlorothiazide (25 mg once or twice daily). Amiloride 5 to 10 mg once or twice daily may be used as an adjunct to thiazides and is especially useful for lithium nephrotoxicity. Nephrogenic DI may respond to combination therapy if one agent is ineffective. Combinations may include indomethacin with hydrochlorothiazide, indomethacin with DDAVP, or indomethacin with amiloride. Although oral indomethacin 25 to 50 mg every 8 hours has been effective, other nonsteroidal antiinflammatory drugs (NSAIDs, tolmetin, and ibuprofen) may be less effective.

40. How quickly should you correct states of water excess or deficiency?

The main concern in therapy for abnormal TBW is prevention of devastating neurologic complications. An understanding of cerebral adaptation to changes in TBW, as outlined in Questions 25 and 26, emphasizes the need for urgent therapy only in the symptomatic patient. The three useful rules in treating disturbances of water (measured by changes in P_{Na}) are as follows:

1. Speed of correction: Return P_{Na} to normal at a speed relative to that by which it became abnormal. If the change in P_{Na} was slow (days), correct it slowly (days). If the change was rapid (minutes to hours), correct it rapidly (minutes to hours).
2. Symptom-driven urgency: If there are no symptoms of water or Na imbalance (see Question 24), there is no immediate urgency. If there are symptoms, there is urgency. Questions 25 and 26 outline the cerebral adaptations to altered tonicity that may cause devastating changes in brain volume. These adaptations also cause the patient's symptoms. Thus, symptoms should drive the clinician to correct the altered tonicity rapidly.
3. Degree of correction: Rapidly correct P_{Na} toward normal levels until symptoms abate, but not to normal.

These concepts—speed, symptoms, and degree of P_{Na} correction—apply to both hyponatremia and hypernatremia (see Question 47).

41. What is the significance of the $[U_{Na} + U_K]/P_{Na}$ ratio?

The $[U_{Na} + U_K]/P_{Na}$ ratio allows for calculating electrolyte-free water excreted per day and is useful in deciding how much water can be consumed without lowering P_{Na}. If the $[U_{Na} + U_K]/P_{Na}$ ratio is >1, the patient is excreting no free water. Thus, all water given to the patient is retained, and free water clearance is negative. Any water consumed would lower P_{Na}. If the ratio is <1, the patient is excreting free water and may consume some free water without decreasing P_{Na}.

For example, if patient A makes 2 L of urine daily and has a U_{Na} value of 20 mEq/L, a UK value of 20 mEq/L, and a P_{Na} value of 135 mEq/L, the patient excretes 1.4 L of electrolyte-free urine. If insensible loss is 800 mL, then patient A could consume 1.4 L + 0.8 L = 2.2 L without a change in the P_{Na}. If patient A had a 1000-mL fluid restriction, the net fluid balance would be 1000 mL – 2200 mL = 1200 mL lost.

However, if patient B makes 2 L of urine and has a U_{Na} value of 130 mEq/L, a U_K value of 60 mEq/L, and a P_{Na} value of 125 mEq/L, patient B makes –1.04 L or retains free water; therefore there is no free water loss. If patient B has the same insensible loss of 800 mL, patient B will retain 204 mL if no additional fluid is allowed. Given the same 1000-mL fluid restriction, patient B would have 1000 mL + 204 mL = 1204 mL net gain in fluid. This net-free water retention would make the hyponatremia worse. The calculations for free water clearance in patients A and B are as follows:

The formula for free water clearance is:

$$CH_2O = V\left(1 - \frac{[U_{Na} + U_K]}{P_{Na}}\right)$$

Patient A:

$$CH_2O = 2\,L\left(1 - \frac{[20 + 20]}{135}\right) = 2\,L(1 - 0.30) = 2\,L \times 0.70 = 1.4\,L$$

Patient B:

$$CH_2O = 2\,L\left(1 - \frac{[130 + 60]}{125}\right) = 2\,L(1 - 1.52) = 2\,L \times (-0.52) = -1.04\,L$$

42. What are vasopressin receptor antagonists, and when would you use them for hyponatremia therapy?

The conventional treatment of hyponatremia—water restriction or saline administration—remains appropriate for most patients. However, vasopressin receptor antagonists (VRAs) like conivaptan and tolvaptan are valuable for treating specific cases of hyponatremia, especially in hospitalized patients with normal extracellular fluid volume (SIADH). Due to their distinct mechanism, these medications are termed *aquaretics*.

Conivaptan is a first-in-class VRA that blocks AVP binding to V1a and V2 receptors in the vasculature and renal tubules, respectively. Blocking V2-R decreases free water reabsorption, increasing excretion, while V1a receptor blockade may cause vasodilation, reducing afterload in congestive heart failure (CHF), though it may negatively impact hemodynamics in cirrhosis. Conivaptan is available in 20-mg/5-mL glass ampules. The recommended dose is a 20-mg IV loading dose over 30 minutes, followed by a continuous 20-mg infusion over 24 hours for 2 to 4 days. If serum sodium does not rise at the desired rate, increase to 40 mg/day. The infusion should not exceed 4 days.

Tolvaptan is a pure V2-R antagonist available in 15-mg and 30-mg tablets for once-daily oral dosing. The dose can be increased from 15 to 30 mg daily to a maximum of 60 mg daily. Like conivaptan, tolvaptan induces selective water diuresis without affecting Na and K excretion. Blocking ADH on the V2-R allows rapid correction of hyponatremia, necessitating careful monitoring of P_{Na} changes to avoid excessively rapid correction. There have been studies and clinical practices involving the long-term use of tolvaptan for refractory hyponatremia due to SIADH, even though it's not FDA-approved for use beyond 30 days. These studies suggest that tolvaptan can be effective and well-tolerated for chronic SIADH when used off-label. However, monitoring for potential side effects and the risk of overcorrection is important.

Additionally, tolvaptan is contraindicated in chronic liver disease, and the 30-day cost of tolvaptan is several thousand dollars. Other V2 receptor antagonists, such as lixivaptan, are in clinical trials but are not yet FDA-approved or available.

43. What is the appropriate P_{Na} correction factor for hyperglycemia?

The standard correction factor is a 1.6-mEq/L decrease in P_{Na} for each 100-mg/dL increase in plasma glucose concentration above 100 mg/dL up to 400 mg/dL. If patients have glucose values >400 mg/dL, the correction factor is 2.4 mEq/L.

CLINICAL PROBLEMS IN WATER METABOLISM

44. A 75-year-old woman presents with confusion but no focal neurologic signs. She has type 2 diabetes mellitus. Blood pressure is 110/54 mm Hg. Pulse is 96 beats/min. Neck veins are not visualized in the supine position. Plasma glucose = 900 mg/dL, P_{Na} = 135 mEq/L, CO_2 = 20 mEq/L, P_{Cr} = 3.0 mg/dL, BUN = 50 mg/dL, U_{Na} = 40 mEq/L; urine glucose is 4+ and urine ketones 3+. What is her fluid and volume status and treatment?

Glucose remains in the ECF because of insulin deficiency and increases ECF tonicity. Greater tonicity pulls water from ICF to ECF, concentrating ICF and diluting ECF until ICF and ECF osmolalities are equal. The osmotic pressure of 900 mg/dL glucose (900 ÷ 18 = 50 mOsm/kg) is the driving force for water movement from ICF to ECF. Water movement from ICF to ECF dilutes the ECF and decreases P_{Na} (translocation hyponatremia). Each 100-mg/dL rise in plasma glucose above 100 mg/dL decreases P_{Na} by 1.6 mEq/L. In this patient, the predicted decrease in P_{Na} = (900 – 100) ÷ 100 × 1.6 = 13 mEq/L. The predicted P_{Na} would be 140 – 13 = 127 mEq/L. However, a more accurate correction factor for elevated glucose values over 400 mg/dL would be 2.4 mEq/L (see Question 43). Thus, the predicted decrease in P_{Na} would be (900 – 100) ÷ 100 × 2.4 = 19 mEq/L. The predicted P_{Na} would be 140 – 19 = 121 mEq/L. But this patient's P_{Na} is 135 mEq/L, suggesting that there has been further water loss from osmotic diuresis and significant dehydration. The effective osmolality is 2(135) + 900 ÷ 18 = 320 mOsm/kg and is compatible with hyperosmolar coma. Because this woman has decreased TBW, decreased blood pressure, and a BUN/Cr ratio that suggests prerenal azotemia, you might expect her to have low U_{Na} and high U_{osm}. However, osmotic diuresis caused by urine glucose, ketones, and urea increases U_{Na} and water, making U_{Na} and U_{osm} less useful markers of dehydration. The flatness of neck veins in the supine position usually results from intravascular volume depletion. Rapid lowering of her glucose to 100 mg/dL will quickly decrease P_{osm}, shift water to ICF, increase P_{Na} by 13 to 19 mEq/L, and potentially cause cerebral edema and cardiovascular collapse. This patient has the hyperglycemic hyperosmolar state (HHS) with mild ketosis, confusion, volume depletion, and an effective osmolarity of 320 mOsm/Kg. Recommendations include ICU admission and administration of 0.9% saline at 500 to 1000 mL/hr for 2 to 4 hours to replace volume with careful monitoring to avoid volume overload. Then, if glucose does not decrease by 50 to 70 mg/dL per hour with fluid management, an IV bolus (0.1 units/kg body weight) of regular insulin should be added, followed by a continuous infusion of regular insulin at 0.1 units/kg per hour, and adjust IV fluids (usually a switch to 0.45% saline) and insulin to avoid changes in P_{osm} >3 mOsm/kg/hr. Follow the protocol for the treatment of HHS.

45. You admit a 35-year-old patient with schizophrenia because of a change in mental function and excessive urine output. U_{osm} = 70 mOsm/kg. P_{osm} = 280 mOsm/kg. 24-hour urine output = 12 L/day. How much free water is the patient excreting each day?

CH_2O is the amount of solute-free water excreted per day. Osmolar clearance (C_{osm}) is the amount of urine excreted per day that contains all the solute that is isosmotic to plasma. When urine is hypotonic to plasma, the total urine volume consists of two components: one part that is free of solute (CH_2O) and the other that is isosmotic to plasma (C_{osm}). To measure how much of the urine is pure (free) water, calculate the CH_2O. To do so, you need to know the C_{osm} and the urine volume (V). The formula for clearance of any substance (including osmoles) is always the same:

$$C = \frac{UV}{P}$$

where C is the volume of plasma cleared of the substance per unit time, U is the urinary concentration of the substance, P is plasma concentration of the substance, and V is total urinary volume per unit time. The calculations for this patient follow:

$$V = C_{osm} + CH_2O$$

$$CH_2O = V - C_{osm}$$

$$C_{osm} = \frac{U_{osm}V}{P_{osm}}$$

$$C_{osm} = \frac{(70\text{ mOsm/kg} \times 12\text{ L/day})}{280\text{ mOsm/kg}} = 3.0\text{ L/day}$$

$$CH_2O = V - C_{osm} = 12\text{ L/day} - 3\text{ L/day} = 9\text{ L/day}$$

Manipulation of formula (2) offers another means of calculating free water clearance, as follows:

$$CH_2O = V\left(1 - \frac{U_{osm}}{P_{osm}}\right)$$

$$CH_2O = 12\text{ L/day}\left(1 - \frac{70}{280}\right) = 9\text{ L/day}$$

Thus, the patient's daily urine output contains 9 L/day of pure (free) water and 3 L/day that is isotonic to plasma. This information does not distinguish primary polydipsia from DI. However, the low P_{osm} (280 mOsm/kg) suggests primary polydipsia.

46. A 45-year-old-man with a 30-pack-year history of smoking presents with cough, dyspnea, fatigue, and a 15-lb weight loss. Chest radiography shows mediastinal adenopathy and right atelectasis with pleural effusion. P_{osm} = 270 mOsm/kg. P_{Na} = 125 mEq/L. U_{osm} = 470 mOsm/kg. U_{Na} = 130 mEq/L. U_K = 60 mEq/L. Urine volume = 1 L/day. How much free water is the patient excreting each day? What is the likely pulmonary lesion?

Urine is hypertonic to plasma if the U_{osm} exceeds P_{osm} or the $U_{[Na+K]}$ exceeds P_{Na}. Urine hypertonic to plasma contains two parts: (1) the volume that would be required to contain all solute and remain isosmotic to plasma is the osmolar clearance (C_{osm}); and (2) the volume of free water that was removed from the isotonic glomerular filtrate to make U_{osm} higher than P_{osm} or $U_{[Na+K]}$ higher than P_{Na} is the negative free water clearance (T^{CH_2O}; see next paragraph). There are two ways to calculate free water clearance: one method uses osmolality, as in Question 45; the other uses electrolytes (Na and K). Electrolyte-free water clearance more accurately estimates free water clearance and negative free water clearance, especially when urine contains large numbers of nonelectrolyte osmolytes, such as urea, that increase osmolality unrelated to free water clearance. To calculate electrolyte free-water clearance, the U_{Na} and U_K concentrations and the P_{Na} are used. Because $U_{[Na+K]}$ is $>P_{Na}$—(130 + 60) >130—the net urinary excretion of free water is negative, and therefore, free water clearance is negative. Calculations for osmolar and electrolyte-free water clearances in this patient follow:

Calculations for classic osmolar (negative) free water clearance:

$$V = C_{osm} - T^{CH_2O}$$

$$T^{CH_2O} = C_{osm} - V$$

$$C_{osm} = 1\text{ L/day}\left[\frac{470}{270}\right] = 1.74\text{ L/day}$$

$$T^{CH_2O} = 1.74\text{ L/day} - 1\text{ L/day} = 0.74\text{ L/day}$$

Manipulation of formula 2 offers another means of calculating negative free water clearance, as follows:

$$T^{CH_2O} = V\left[\frac{U_{osm}}{P_{osm}} - 1\right]$$

$$T^{CH_2O} = 1\,\text{L/day}\left[\frac{470}{270} - 1\right] = 0.74\,\text{L/day}$$

Calculations for electrolyte-free water clearance (negative free water clearance) are as follows:

$$T^{CH_2O} = C_{[Na+K]} - V$$

$$C_{[Na+K]} = \left[\frac{C_{[Na+K]}}{P_{Na}} \times V\right]$$

$$C_{[Na+K]} = \left[\frac{190\text{ mEq/L}}{125\text{ mEq / L}} \times 1\ \text{L/day}\right] = 1.52\,\text{L/day}$$

$$T^{CH_2O} = 1.52\,\text{L/day} - 1\ \text{L/day} = 0.52\,\text{L/day}$$

Thus, the patient's kidneys add (by water reabsorption) 520 to 740 mL of free water to plasma each day. With a low P_{osm}, it is inappropriate to retain water. This finding suggests SIADH. Volume depletion, adrenal insufficiency, and hypothyroidism must be excluded before making the diagnosis of SIADH. This patient had small cell carcinoma of the lung with ectopic ADH secretion. SIADH develops in 15% of patients with small cell carcinoma of the lung. This tumor is highly associated with smoking and accounts for 15% to 25% of lung cancer. Other lung cancers rarely secrete ADH.

47. A 34-year-old, 60-kg woman presents 12 hours after discharge following cholecystectomy. She has a headache, confusion, muscle cramps, weakness, lethargy, agitation, nausea, and vomiting. She had no symptoms at discharge. P_{Na} is 110 mEq/L. What has caused the hyponatremia, and how quickly should you treat it?

The patient's hyponatremia was likely caused by drinking too much free water after her surgery, along with ADH release induced by pain and postoperative medications. According to this history, hyponatremia developed acutely (<48 hours), and the patient presents with severe symptoms of hyponatremia. Risk of cerebral edema is high, and risk of osmotic demyelination syndrome from treatment is low. Therefore treatment should begin immediately in the emergency department, and then the patient should be transferred to the ICU. In this setting of acute symptomatic hyponatremia, the goal of therapy is to increase P_{Na} rapidly by 4 to 6 mEq/L and then more gradually, once the symptoms have improved, to a P_{Na} of about 130 mEq/L. This is best done by administering 2 to 3 boluses (100 cc each) of 3% saline intravenously over 10 minutes, each bolus followed by 3% saline at 1 to 2 mL/kg/hr until P_{Na} increases to the expected goal. A 1- to 2-mL/kg/hr infusion of 3% saline will usually increase P_{Na} by about 1 to 2 mEq/hr. P_{Na} should be measured every 2 to 4 hours to monitor progress and to guide therapy. To guide replacement of water and electrolyte losses in urine, U_{Na} and U_K measurements should be ordered, as needed, especially if P_{Na} is not changing at the expected rate. In acute hyponatremia, if the patient's symptoms are mild to moderate, a slower rate of correction with fluid restriction and/or 3% saline at 1 to 2 mL/kg/hr until P_{Na} is 130 mEq/L would be reasonable, followed by fluid restriction with increased oral sodium intake until P_{Na} returns to normal. The calculations for water excess and the amount of 3% saline necessary to correct the P_{Na} to 120 mEq/L in this patient are as follows:

$$\begin{aligned}\text{Water excess} &= \left(\frac{\text{normal } P_{Na} - \text{observed } P_{Na}}{\text{normal } P_{Na}}\right) \times \text{TBW}\\ &= \left(\frac{140-110}{140}\right) \times 0.5 \times 60\text{ kg}\\ &= 0.21 \times 30\text{ L}\\ &= 6.3\text{ L excess in TBW}\end{aligned}$$

$$\begin{aligned}\text{Na deficit} &= (\text{desired } P_{Na} - \text{observed } P_{Na})\\ &= (120-110)\times 0.5\times 60\text{ kg}\\ &= 10\text{ mEq/L}\times 30\text{ L}\\ &= 300\text{ mEq Na}\end{aligned}$$

Knowing the Na deficit is useful clinically because Na can be replaced at a controlled rate to improve the hyponatremia. The Na in 3% saline is 513 mEq/L:

$$\frac{300\text{ mEq Na}}{513\text{ mEq/L}} = 0.585\text{ L}$$

Assuming no Na or water would be lost in urine, giving 585 mL of 3% saline will correct this patient's P_{Na} to 120 mEq/L. A similar calculation for 3% saline to infuse to increase P_{Na} by 6 mEq/L is as follows: A 6 mEq/L increase in P_{Na} in a woman with a weight of 60 kg, which is 50% water, would require: 6 mEq/L × 0.5 × 60 kg = 180 mEq Na. Because 3% saline has 513 mEq/L sodium, 0.351L (180 mEq Na ÷ 513 mEq/L) or 351 mL of 3% saline would be required to increase the P_{Na} by 6 mEq/L. Thus, three boluses of 100 cc of 3% saline empirically given over 10 minutes each would correct P_{Na} by about 6 mEq/L over the 30 to 40 minutes needed to give the three boluses.

48. An 80-year-old woman who rarely leaves her home is brought to the hospital after being found in a confused state. Three weeks ago, she had seen her physician, who started her on a diuretic for systolic hypertension. On arrival, her P_{Na} is 110 mEq/L. What is the cause of her hyponatremia?

Because of aging, elderly patients lose GFR, concentrating ability, and diluting ability. Thus, an 80-year-old woman may have a normal (for age) renal-concentrating range of 100 to 700 mOsm/kg. However, maximal U_{osm} in the elderly may be as low as 350 mOsm/kg. This woman's average diet may generate only 600 mOsm/day. Her normal range of urine output would then be 0.9 to 6.0 L/day. If her dietary intake fell to 300 mOsm/day, her maximal urine output would fall to 3 L/day, calculated as follows:

$$300\text{ mOsm/day} \div 100\text{ mOsm/kg} = 3\text{ L/day}$$

Given free access to water and a thiazide diuretic, which impairs urinary dilution, she could easily become water intoxicated and hyponatremic. The mechanism of hyponatremia in beer potomania and the "tea-and-toast diet" is low total osmolar intake and relatively increased water intake. The decreased osmotic load for excretion limits the amount of water excreted. This patient's hyponatremia is probably chronic; however, her only symptom is confusion—so she is considered mild to moderately symptomatic. The mild symptoms with severe hyponatremia also suggest chronicity. If the duration is known to be >48 hours or if the duration of the hyponatremia is not clear in an outpatient setting, it is likely that the symptoms are chronic, and it would be safest to treat for chronic hyponatremia, given the high risk for osmotic demyelination syndrome (ODS). Computed tomography (CT) or MRI would be appropriate modalities to use in this patient in a confused state and might change therapy if the presence of cerebral edema is revealed. To avoid ODS in this patient and in high-risk individuals, the rate of P_{Na} correction to a goal of 130 mEq/L should be slow and average no more than 4 to 6 mEq/L during the first 24 hours and 8 mEq/L per each additional 24-hour period. For normal-risk individuals, correction rates can be 4 to 8 mEq/L in the first 24 hours and 8 mEq/L in any subsequent 24-hour period. Treatment of this patient should consist of discontinuation of the thiazide diuretic and fluid restriction until symptoms further improve or the P_{Na} is 130 mEq/L. Symptoms, signs, and P_{Na} should be assessed frequently. Remember: elderly women taking thiazide diuretics, those who have alcoholism, malnourished patients, those with hypokalemia, and burn victims are at particular risk for ODS.

WEBSITES

American Academy of Family Physicians: Diagnosis and management of sodium disorders: hyponatremia and hypernatremia: https://www.aafp.org/afp/2015/0301/p299.html.
EMedicine: SIADH review: http://www.emedicine.com/ped/topic2190.htm.
EMedicine: Hyponatremia review: http://www.emedicine.com/med/topic1130.htm.
EMedicine: Lithium nephropathy review: http://www.emedicine.com/med/topic1313.htm.
EMedicine: Diabetes insipidus review: http://www.emedicine.com/med/topic543.htm.

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CHAPTER 31

Disorders of Growth

Philip Zeitler

1. Summarize normal growth velocity for children until the pubertal growth spurt.

- First 6 months: 16–17 cm
- Second 6 months: approximately 8 cm
- Second year: just over 10 cm
- Third year: approximately 8 cm
- Fourth year: 7 cm
- Later childhood until puberty (5–10 years): growth averages 5–6 cm/year

2. Summarize growth velocity during the pubertal growth spurt.

Maximum growth rate is 11–13 cm/year.

In girls, a growth spurt occurs early in puberty (breast Tanner stage II).

The growth spurt is later in boys (pubic hair Tanner stage III–IV, testicular volume 12–15 mL).

Some children may experience a transient period of slow growth just before the onset of puberty (prepubertal slowing).

3. How is height measured accurately?

- The most essential tool for the detection of growth abnormalities is the ability to obtain accurate and reproducible height measurements. This requires the availability of appropriate equipment as well as proper positioning of the child.
- At all ages, children should be measured at full stretch with a straight spine because this is the only position that will be reproducible.
- Children should be shoeless, and hair decorations or braids need to be removed if they interfere with the positioning of the stadiometer.
- Scales with floppy arms are unreliable.

4. What technique is used for infants up to 2 years of age?

Supine length should be measured in infants and children up to 2 years of age. Accurate measurement requires a supine stadiometer, a boxlike structure with a headboard, and a movable footplate. Two people are needed, one holding the infant's head against the headboard while the other straightens the legs and places the ankles at 90 degrees against the movable footplate. The length is read from the attached measuring device, or marks are made for measurement by tape measure.

5. Describe the technique for children 2 years of age and older.

- Standing height is measured. Accurate measurement requires a stadiometer with a rigid headboard, footplate, and backboard.
- The child stands against the backboard, with heels, buttocks, thoracic spine, and head touching.
- The measurer exerts upward pressure on the child at the angle of the jaw to bring the spine into full stretch, and the headboard is lowered until it touches the top of the head. A counter reads the measurement.
- If a stadiometer is not available, the child should stand against a wall in the same position as used for a stadiometer. A rigid right angle is moved downward to touch the top of the head, and a mark is made and measured.
- Weight and head circumference (when appropriate) should be recorded.

6. How is height recorded?

The second critical tool for the evaluation of growth is the standardized growth curve, and all measurements should be plotted rather than just recorded in the chart. A carefully constructed and up-to-date growth curve is critical to the recognition of growth abnormalities. Furthermore, the more points that are plotted on the curve, the greater the understanding of the child's growth. Thus, efforts should be made to obtain growth measurements at all patient contacts, including illness visits, because well-child visits are infrequent during the middle childhood years when growth abnormalities are most common.

7. List the common errors in plotting growth charts.

Errors in plotting growth points are a frequent cause of apparent growth abnormalities. Common errors include:

- Plotting the wrong height (e.g., plotting inches instead of centimeters)
- Not plotting the child's height at the exact chronologic age (height should be plotted to the nearest month or decimal age)
- Use of an inappropriate growth chart

8. What is meant by "appropriate growth chart"?

Numerous growth charts are available, and careful consideration should be given to the appropriate chart for a particular child at a particular time. Commonly available growth charts include:

- Charts for plotting supine length (the 0–36-month charts in common use)
- Charts for plotting stature (i.e., standing height) (2–18-year charts)

Other specific growth charts should be used when appropriate:

- Ethnic-specific charts
- Growth charts specific for common syndromes (e.g., Turner syndrome, Down syndrome, achondroplasia) should be used when appropriate.

9. How do age and position affect growth measurements?

- A child measured supine is slightly longer than the same child measured standing up.
- Charting of a standing child on a supine chart gives the erroneous impression of decreased growth velocity. This is a common cause of apparent growth abnormality in children aged 2–3 years who are measured standing up for the first time but whose measurements continue to be plotted on the supine chart.

10. What historic information is necessary for interpreting a growth chart?

- Birth history and birth weight
- Attainment of developmental milestones
- History of chronic illnesses
- Medication exposure
- History of surgery or trauma
- Current symptoms, if any
- Height of biological parents and family history of significant short stature
- Timing of parental puberty and family history of significant pubertal delay

11. What physical examination findings help interpret a growth chart?

- Signs of chronic illness
- Stigmata of a syndrome
- Specific signs of hormonal abnormality (thyroid deficiency, growth hormone [GH] deficiency, and glucocorticoid excess)

12. How does radiologic imaging help interpret a growth chart?

- A bone-age film can provide important information about skeletal maturity. The degree of skeletal maturity is an important determinant of remaining growth potential and can help estimate expected height in children developing more slowly or more rapidly than their peers.

KEY POINTS 1: GENERAL GROWTH

- Proper evaluation of growth depends on accurate measurement of height and correct plotting of measurements on the appropriate growth curve.
- Common errors in plotting include plotting the wrong height, not plotting the child's height at the exact chronologic age, and use of an inappropriate growth chart.
- An abnormal growth velocity for age generally distinguishes growth abnormalities from normal growth variants.
- Apparent abnormalities in growth are most frequently due to normal growth variants. Poor growth secondary to chronic medical illness is the next most frequent cause. Hormonal causes are less frequent.
- A radiograph of the left hand and wrist is obtained in children aged over 2 years and maturation of epiphyseal centers is compared with available standards.

13. Explain the significance of parental target height or "mid parental height."

Parental height helps determine expected adult height on the basis of genetic potential. Add the parents' heights in centimeters; add 13 cm if the child is male and subtract 13 cm if the child is female; then divide by two. The resulting mid parental height ±5 cm gives the expected 10th to 90th percentile for the offspring of those parents.

14. What is the most important factor in identifying an abnormal growth curve?

An abnormal growth velocity for age generally distinguishes growth abnormalities from normal growth variants. Although there are many causes of short stature, including genetics, short normal children grow normally, whereas children with a problem almost always have an abnormal growth velocity. For example, a child with a stature in the 5th percentile who is growing with a normal growth velocity is less worrisome than a child whose stature has fallen from the 90th to the 75th percentile, even though the latter is taller than the former. Growth velocity abnormalities may, however, be subtle.

15. What causes abnormal growth in children?

Abnormalities in growth are most frequently due to either normal growth variants (familial short stature or constitutional delay of growth and puberty) or underlying chronic medical illness, either recognized or unrecognized. Hormonal causes are less frequent.

16. Which syndromes are associated with abnormal growth?

- Down syndrome
- Prader-Willi syndrome
- Turner syndrome
- Noonan syndrome
- Other chromosomal abnormalities

17. List nonendocrine diseases and treatments that may be associated with poor growth.

- Malnutrition
- Pulmonary disease (cystic fibrosis, asthma)
- Cardiac disease
- Rheumatologic disease
- Gastrointestinal disease (Crohn's disease, inflammatory bowel disease)
- Neurologic disease (ketogenic diet, stimulant medications)
- Renal disease
- Anemia
- Neoplasia
- Long-term glucocorticoid use

18. Using the tools of growth curve, bone age, and height, how does one distinguish between familial (genetic) short stature and other causes?

Children with familial short stature grow at a normal velocity for age but with stature below the normal curve. They also grow within the expected target height percentile (i.e., they are as tall as expected for their genetic potential). If a child's projected height (by extrapolation of the growth curve along the current percentile) falls within the target range, the likelihood is high that the current height is explained by genetic factors. Children with familial short stature also have a bone age approximately equal to chronologic age.

19. Give an example of distinguishing familial short stature from other causes of short stature.

A 5-year-old whose height is below the third percentile, whose growth has traced a line parallel to the third percentile, whose height projects within the parental target range, and whose bone age is also 5 years is likely to have familial short stature. However, if the growth velocity is abnormal or the projected height falls below the predicted range, other factors may be involved in the short stature (Figs. 31.1 and 31.2).

20. Other than familial short stature, what is the most common cause of short stature?

Constitutional delay of growth (constitutional short stature or "late bloomer"), which affects up to 2% of children, is characterized by short stature and delayed bone age and represents a normal growth pattern simply shifted to a later age. Affected children typically have a period of subnormal growth between 9 and 30 months of age, followed by normal growth velocity throughout the remainder of childhood. In accord with the delayed developmental pattern, bone age is delayed. The continuing growth delay also results in a delay in pubertal development and physical maturity. Such children (more often boys) generally have a family history of a similar growth pattern and may have a more dramatic deceleration of growth velocity before they enter puberty than normal children. They complete their growth at a later age, reaching an adult height within the expected genetic potential (Fig. 31.3).

21. How is the diagnosis of constitutional delay of growth made?

The diagnosis of constitutional delay of growth based on the following criteria does not require further laboratory support:

- Period of slowed growth in the second year of life with downward crossing of percentile.
- Normal growth velocity during childhood but with stature below the expected percentile for family.
- Delayed bone age
- Height prediction appropriate for the family (plot the current height at the patient's bone age and follow the resulting percentile to adult height. In constitutional delay, this generally leads to a projected height within the parental target range.)
- Positive family history, delayed dentition, and delayed puberty in adolescence.

22. What is the effect of testosterone therapy on boys with constitutional delay of growth?

Short-term testosterone therapy for boys with constitutional delay (75–100 mg of long-acting testosterone esters given once a month for 6 months) accelerates growth and stimulates pubertal development without compromising final adult height or advancing bone age. Clinically, the boys experience pubertal changes, including genital enlargement (but not testicular growth), growth of pubic and axillary hair, deepening of voice, body odor, and acne. There may be personality changes characteristic of early puberty as well.

23. List the endocrine causes for short stature in children, in order of prevalence.

- Hypothyroidism: congenital or acquired
- GH deficiency
- Glucocorticoid excess: iatrogenic or endogenous (less common)
- Pseudohypoparathyroidism

24. What laboratory measurements should be considered in evaluating a patient for short stature?

Laboratory tests should be designed to achieve two goals: (1) exclusion of undiagnosed chronic illness and (2) exclusion of specific disorders associated with poor growth.

25. Which laboratory tests help exclude undiagnosed chronic illness?

- Electrolyte measurements
- Blood urea nitrogen/creatinine measurement
- Liver transaminase measurements
- Complete blood count
- Erythrocyte sedimentation rate (ESR) measurement

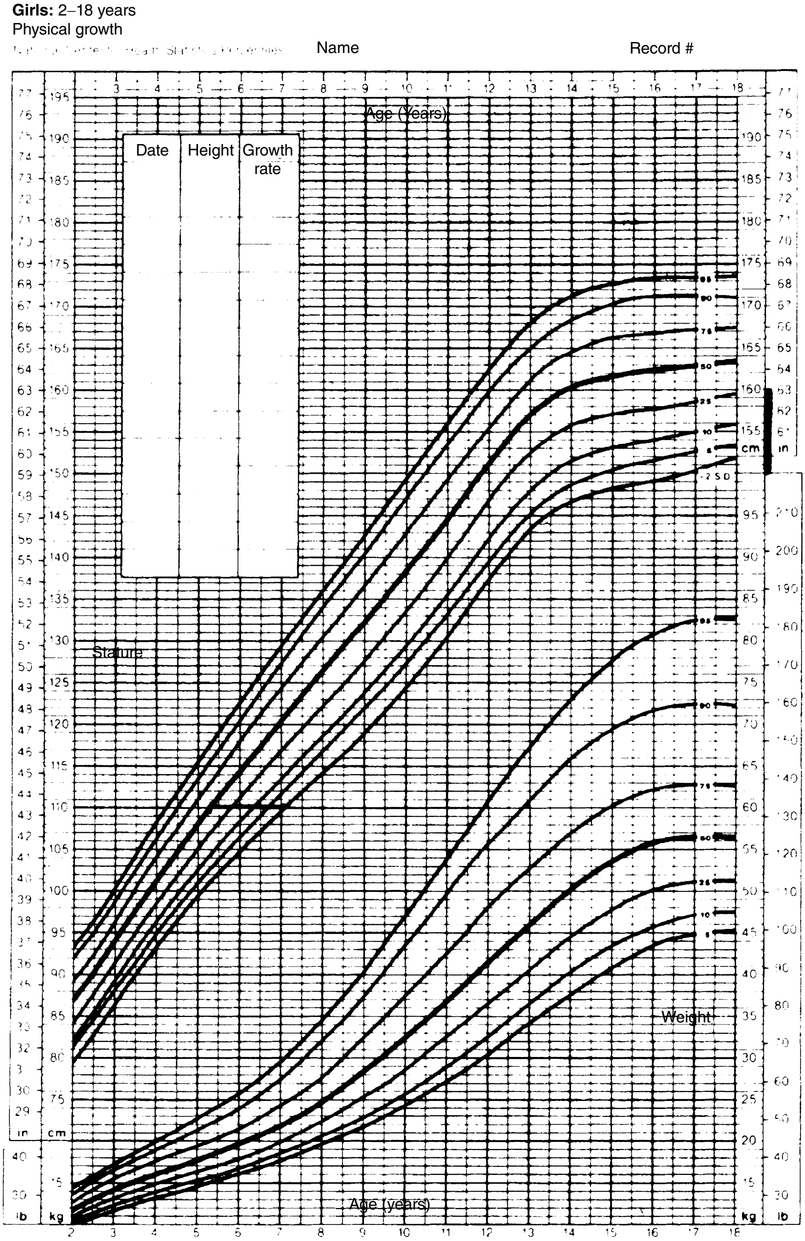

Fig. 31.1 Growth chart for a 7-year-old girl with a height of 110 cm. Height age = 5 years, 3 months; bone age = 7 years; father's height = 65 inches (165 cm); mother's height = 62 inches (157 cm); corrected mid-parental height (± 1 SD) = 155 ± 5 cm; predicted adult height = 60 inches. The child has a predicted adult height within genetic potential and a bone age equal to chronologic age. She has a genetic or familial short stature.

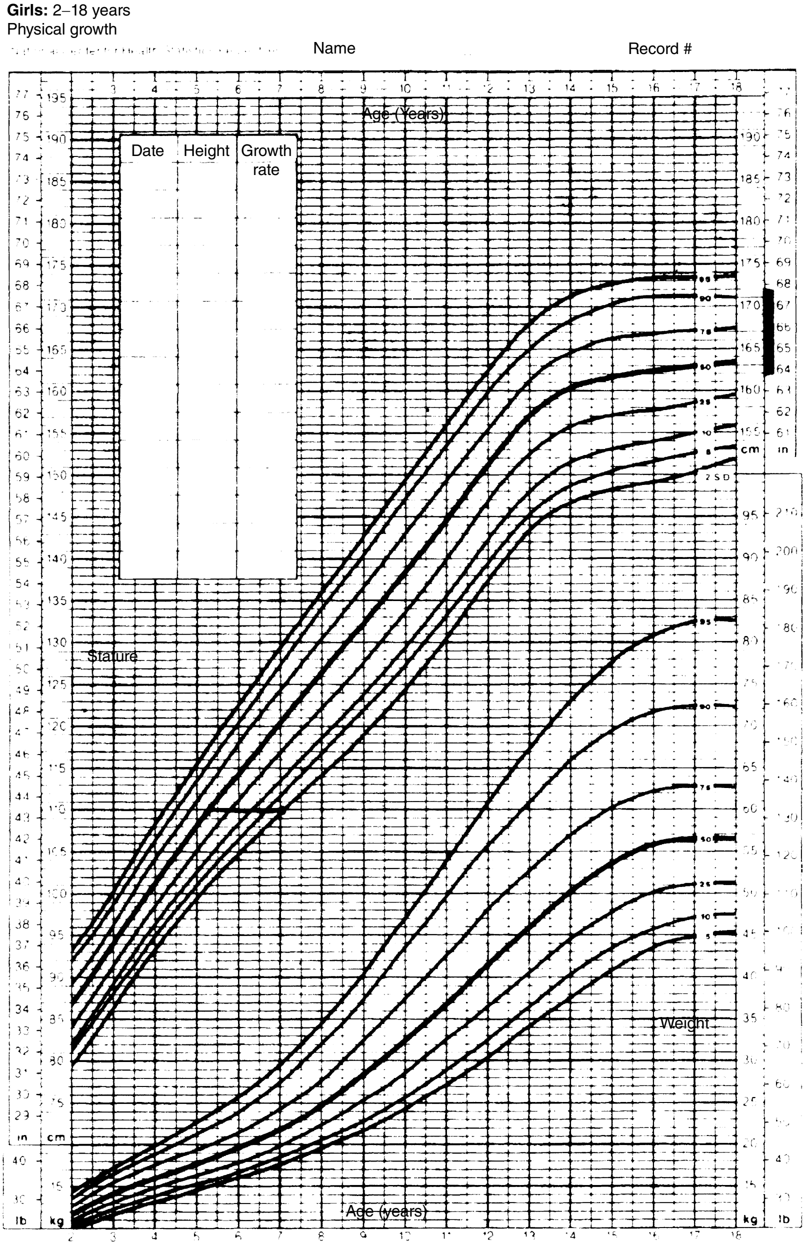

Fig. 31.2 Growth chart for a 7-year-old girl with a height of 110 cm. Height age = 5 years, 3 months; bone age = 5 years; father's height = 70 inches (178 cm); mother's height = 66 inches (168 cm); corrected mid-parental height (± 1 SD) = 167. 5 ± 5 cm. The child is growing below the fifth percentile, but an extrapolation of her growth curve to adult height gives a final height below genetic potential. Clearly, her height cannot be attributed to genetic short stature alone.

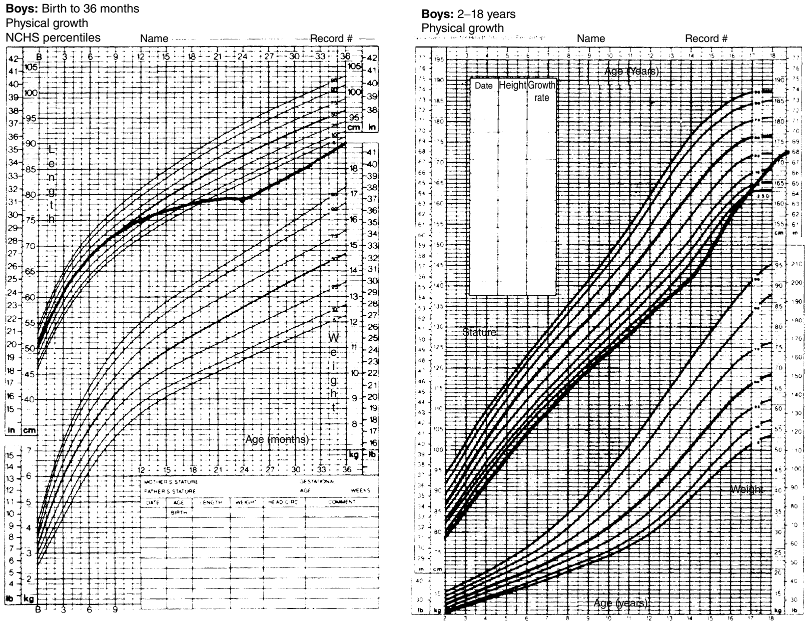

Fig. 31.3 Growth charts for a patient with constitutional delay of growth. Subnormal velocity during the second year of life (*left chart*) followed by normal velocity through childhood and a prolonged growth period with the eventual achievement of normal adult height (*right chart*).

26. Which laboratory tests help exclude gastrointestinal disorders associated with poor growth?

Because symptoms may be limited, the following tests are recommended:

- Celiac antibody (anti-tissue transglutaminase) test
- Inflammatory bowel disease screen if the child has an elevated ESR or anemia

27. List the laboratory tests for genetic disorders associated with poor growth.

- Karyotype (Turner syndrome), considered in all short girls
- Fluorescence in situ hybridization (FISH), for Prader-Willi syndrome
- Genetic test for PTPN11 mutation, for Noonan syndrome

28. Which hormonal disorders should be excluded by laboratory results?

- Thyroid deficiency (thyroid-stimulating hormone [TSH] and total or free thyroxine [T4])
- GH deficiency (see question 30)

29. Describe the causes of GH deficiency.

Most cases of GH deficiency are isolated and idiopathic. Idiopathic GH deficiency affects as many as 1:10,000 to 1:15,000 children. It is sporadic in the great majority of cases, but a rising number of specific gene mutations involved in the synthesis of GH or the regulation of its secretion are being reported. Other important underlying causes are listed in the following sections.

30. How is GH deficiency diagnosed?

The diagnosis of GH deficiency is primarily a clinical one, aided by laboratory support, rather than a diagnosis based on definitive testing. Most important is identifying the child in whom such a diagnosis would be appropriate. Children with subnormal growth should be evaluated for GH deficiency only after a thorough search fails to reveal any other cause for growth delay.

31. List the components of the laboratory evaluation for GH deficiency.

- Measurement of serum insulin-like growth factor 1 (IGF-1)
- Measurement of IGF-binding protein 3 (IGFBP3) may be useful in limited specific clinical situations (infancy, poor nutritional state) because IGF-1 may be low for reasons other than GH deficiency in these circumstances.
- GH stimulation testing

32. Why is the serum level of IGF-1 important?

IGF-1 is a GH-dependent protein produced in the liver in response to pulsatile GH secretion from the pituitary gland. The serum IGF-1 level reflects liver production of IGF-1 and gives an indirect indication of GH secretion. The following characteristics of IGF-1 should be kept in mind when analyzing the serum IGF-1 level:

- Serum IGF-1 levels remain constant during the day, unlike GH levels.
- Serum IGF-1 levels vary with age, and the reported value must be compared with appropriate age-specific and pubertal stage-specific norms available from performing laboratories.
- Low serum IGF-1 levels (>2 SD below mean for age) are 70–80% predictive of low values on more rigorous tests of GH secretion, as long as other causes of low IGF-1 (e.g., poor nutrition, hypothyroidism, and liver disease) have been excluded.

33. Does a normal level of IGF-1 exclude GH deficiency?

No. A normal IGF-1 level is reassuring but does not rule out GH deficiency in a suggestive clinical context.

34. Does a low serum level of IGF-1 confirm the diagnosis of GH deficiency?

No. Poor nutrition, chronic disease, and hypothyroidism suppress IGF-1 levels. In addition, before the age of 6 years, the IGF level is low, and the overlap between normal and GH-deficient levels renders its measurement highly insensitive. Measurement of IGFBP3 may be useful in this situation, although this test is less sensitive than IGF-1 in identifying likely GH deficiency.

35. How is GH testing done?

Because the secretion of GH is episodic, random measurements are not helpful for the diagnosis of GH deficiency. GH must be formally measured in response to a series of stimuli. Various pharmacologic agents are used, but there is no consensus about which is optimal. The child must have fasted overnight, must be euthyroid, and must have no underlying chronic disease. In addition, at least two tests using different stimulating agents are generally performed.

36. How are the results of GH testing interpreted?

The normal GH response to stimulation testing depends on the stimulation test and the type of GH assay used. Failure of the responses to all tests with values at least equal to those expected for normal children is consistent with the diagnosis of classic GH deficiency.

Criteria for the diagnosis of partial GH deficiency and of neurosecretory dysfunction (normal pituitary response to stimuli but low IGF-1, suggesting that endogenous GH secretion is impaired) are less well established.

37. How is idiopathic GH deficiency diagnosed?

GH deficiency can be isolated or associated with other pituitary hormone deficiencies. It can be congenital or can result from trauma or an intracranial neoplasm. All people diagnosed with GH deficiency should undergo cranial imaging unless the cause of the deficiency is previously known. Isolated GH deficiency without an identifiable anatomic or physiologic etiology is considered idiopathic.

38. How is GH deficiency treated?

GH for administration is available through recombinant DNA technology; the majority of children are treated with six or seven daily shots per week at a total weekly dose of 0.18–0.30 mg/kg administered subcutaneously. Because the effect of GH wanes after several years of therapy, it is common to see dramatic catch-up growth (approximately 10–12 cm/year) in the first or second year of therapy, followed by velocities ranging from normal to 1.5 times normal in subsequent years. Weekly formulations of GH are now available that offer the convenience of dosing with similar responses.

39. What is the prognosis for adult height in treated children with GH deficiency?

Although nearly all treated children reach an adult height significantly better than predicted before therapy is initiated, many do not reach their predicted genetic potential. Children diagnosed and treated at earlier ages have better height prognoses than those whose therapy is initiated later. Similarly, the more mature the skeleton at diagnosis, the poorer the final outcome.

40. When is GH therapy discontinued?

In children with GH deficiency, the point of diminishing benefit of therapy correlates with skeletal maturity rather than chronologic age or duration of therapy. Therapy is often discontinued at a bone age of 15 years (96% of growth) to 16 years (98% of growth) in boys and 14 years (98% of growth) in girls. However, given what is known about the effects of GH deficiency in adulthood, some patients with severe deficiency may benefit from lifelong hormonal replacement.

41. What other syndromes are considered indications for GH therapy?

GH is now approved by the US Food and Drug Administration (FDA) for the treatment of short stature in the following conditions:

- Chronic renal insufficiency before transplant
- Turner syndrome (45XO or mosaic variants)
- SHOX mutations
- Acquired immunodeficiency syndrome–related wasting syndrome
- Prader-Willi syndrome
- Noonan syndrome
- Short stature due to intrauterine growth retardation in the absence of catch-up growth
- Idiopathic short stature in boys with predicted adult height less than 63 inches and girls with predicted height less than 59 inches (normal GH secretion)

Indications 2 through 6 do not require a demonstration of GH deficiency. The use of GH for the treatment of idiopathic short stature remains controversial among pediatric endocrinologists.

42. What is the prognosis for girls with Turner's syndrome treated with GH?

Girls with Turner syndrome generally demonstrate a significant increase in predicted adult height, with an average increase of 8.8 cm. The overall effectiveness of GH therapy, like that in GH deficiency, depends on chronologic age and bone age at initiation of treatment and on the duration of treatment. Because GH therapy in Turner syndrome normalizes height in younger girls, estrogen replacement therapy can be initiated at an age similar to the age of puberty of the child's peers.

43. What are the potential risks of GH therapy?

The side effects of GH therapy can be divided into three categories: (1) common but clinically unimportant, (2) uncommon with potential clinical importance, and (3) rare or theoretical.

44. List the common but clinically unimportant side effects of GH therapy.

- Acute correction of body water deficit after initiation of GH in deficient children may lead to transient peripheral edema, headache, and joint aches and stiffness.
- Increased average glucose concentration
- Increased systolic blood pressure

45. List the uncommon side effects with potential clinical importance.

- Pseudotumor cerebri
- Slipped capital femoral epiphysis
- Overt glucose intolerance
- Worsening of underlying scoliosis

46. What rare or theoretical side effects may be associated with GH therapy?

- Risk for tumor recurrence or development of a secondary neoplasm: the most recent analyses indicate no increase in the risk of tumor recurrence or development of secondary neoplasms in childhood cancer survivors treated with GH.

- Analysis of a large French database has suggested a possible increase in cancer–related mortality in adults treated with GH as children. This report is not yet confirmed, and the regulatory agencies have not changed labeling in response to this report.

47. Should children with idiopathic short stature (without GH deficiency) be treated with GH?

The FDA has approved the use of GH in children with idiopathic short stature, with a predicted adult height of less than 63 inches (160 cm) for boys and less than 59 inches (150 cm) for girls. However, the use of GH in children in whom no hormonal abnormality can be demonstrated continues to be controversial among pediatric endocrinologists. Short-term studies involving small cohorts have demonstrated a consistent increase in growth velocity with GH therapy in such children. Several studies that monitored children to final height disagreed about the overall effectiveness of therapy. However, most studies agree that the increase in final adult height is limited and can be obtained only at a significant financial cost. The decision to use GH in such children should be carefully considered and requires a thoughtful dialogue among the child, family, and an experienced pediatric endocrinologist who knows the child well.

48. How does the pattern of growth in children with excessive glucocorticoids differ from the pattern in children with exogenous obesity?

Glucocorticoid excess, whether iatrogenic (common) or intrinsic (rare), results in impairment of linear growth. The mechanism reflects increased protein catabolism, increased lipolysis, and a decline in collagen synthesis. Glucocorticoids also suppress the pulsatile release of GH from the pituitary gland and the production of IGF-1 at the target organ. The net result is that children with steroid excess are frequently short. They also have an increased weight-to-height ratio and appear obese. Children with exogenous obesity, on the other hand, generally show accelerated linear growth; thus, they are not only obese but also tall for age.

49. What conditions are associated with excessive growth in childhood?

Relatively few conditions result in overgrowth during childhood. These include familial tall stature (stature appropriate for the parental target), constitutional advanced growth, hormonal causes, and genetic syndromes.

50. Explain constitutional advanced growth.

Constitutional advanced growth is associated with advanced bone age, accelerated growth, and early puberty, with predicted adult height appropriate for the parental target (see question 21). It is essentially normal puberty occurring at the early end of the normal range; obesity and/or familial pattern(s) may be involved.

51. List the hormonal causes of excessive growth.

- Hyperthyroidism
- Androgen excess
- GH excess (pituitary gigantism)
- Estrogen excess

52. Summarize the characteristics of GH excess in childhood.

GH excess is rare in children, in whom it causes tall stature (gigantism) rather than the bony overgrowth seen in adults (acromegaly). Diagnosis is based on the following laboratory results:

- Elevated values on random measurements of GH
- Extremely high levels of IGF-1
- Lack of suppression of GH during a standard glucose tolerance test

53. With what findings is androgen excess associated?

- Precocious puberty in boys
- Congenital adrenal hyperplasia
- Androgen-producing tumors

54. With what findings is estrogen excess associated?

- Precocious puberty in girls
- Estrogen-producing tumors

55. List the genetic syndromes associated with excessive growth.

- Klinefelter syndrome (47,XXY): tall stature, small testes, delay of puberty
- Connective tissue disorders
- Marfan syndrome: tall stature, arachnodactyly, joint laxity, lens displacement
- Stickler syndrome
- Soto syndrome (cerebral gigantism): macrocephaly, progressive macrosomia, dilated ventricles, retardation, advanced bone age
- Beckwith-Wiedemann syndrome: macroglossia, umbilical hernia, hypoglycemia, macrosomia in infancy
- Homocystinuria: arachnodactyly, retardation, homocysteine in urine

KEY POINTS 2: GROWTH VARIANTS

- Children with familial short stature grow at a normal velocity for age and within their expected target height percentile and have a bone age approximately equal to chronologic age.
- Children with constitutional delay of growth have a period of slow growth in the second year of life but then grow with a normal growth velocity.
- Children with constitutional delay of growth also have delayed bone age, height prediction appropriate for the family, and delayed entry into puberty.
- The diagnosis of a growth variant does not require laboratory confirmation, but growth should be followed over time to confirm the initial impression.

KEY POINTS 3: GROWTH HORMONE DEFICIENCY

- GH deficiency is a clinical diagnosis.
- Other causes of poor growth should be excluded.
- Laboratory testing is supportive and confirmatory.
- Laboratory measures include measurement of serum IGF-1 and GH stimulation testing.

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Growth Hormone Use and Abuse

Homer J. LeMar, Jr.

CHAPTER 32

1. What is growth hormone (GH)?

GH is the most abundant hormone produced by the anterior pituitary gland; it is a single-chain peptide hormone produced and secreted by somatotroph cells in the anterior pituitary gland in two molecular forms: the 22-kDa GH is more abundant than the 20-kDa form, but both have similar biologic activity. Measurement of individual GH isoforms plays a key role in the detection of doping in athletes. Endogenous GH production is highest during puberty, and by middle age, decreases to only about 15% of peak levels.

2. How does GH secretion occur?

GH is secreted in a pulsatile fashion, mostly at night. Factors that increase GH secretion include sleep, exercise, trauma, and sepsis. Obesity and increasing age decrease GH secretion.

3. How is the release of GH regulated?

GH secretion is stimulated by GH-releasing hormone (GH-RH) and inhibited by somatostatin, both from the hypothalamus. Ghrelin, a gastric-derived peptide, also stimulates GH release. Another major regulator of GH production is insulin-like growth factor-1 (IGF-1), which acts at the pituitary to directly inhibit GH production, and at the hypothalamus to inhibit the production of GH-RH and to stimulate somatostatin.

4. List the actions of GH.

As the name implies, GH stimulates both linear growth and growth of internal organs (Table 32.1).

5. Does GH exert all of its effects directly?

No. Many of the effects are mediated by IGF-1, which is also called somatomedin C. GH stimulates the production of IGF-1 in peripheral tissues, particularly the liver. In patients with GH resistance, often caused by GH receptor mutations, some effects of GH can be achieved by IGF-1 administration; IGF-1 has been approved for the treatment of GH-resistant patients.

6. What causes excessive GH secretion, and what are the consequences?

The major cause of excessive GH secretion is a GH-producing pituitary tumor. GH excess during childhood results in gigantism. Numerous historical examples have been noted, including Robert Wadlow, the “Alton giant,” who reached a height of just over 8 feet 11 inches and wore size 37AA shoes. GH excess after epiphyseal closure results in acromegaly.

7. What conditions are associated with GH deficiency?

GH deficiency can be congenital (genetic mutations) or may result from damage to the pituitary gland from intracranial tumors, surgery, radiation therapy, trauma, and a variety of infiltrative and infectious diseases. Adult-onset GH deficiency is much less common than that occurring during infancy and childhood and is often related to a preceding event, such as radiation exposure or trauma.

8. What are some common signs and symptoms of GH deficiency?

GH deficiency in childhood results in short stature; similar effects are seen in GH resistance. GH deficiency in adults causes increased adiposity, decreased lean body mass, decreased bone density, decreased extracellular water, reduced cardiac function, decreased muscle force and strength, and diminished exercise performance. Patients have reduced exercise capacity and strength levels and often complain of lethargy and fatigue. Quality of life may be diminished, with manifestations

TABLE 32.1 Actions of Growth Hormone at Specific Sites

TARGET SYSTEM	ACTIONS
Liver and muscle	Increase nitrogen retention, amino acid uptake, and protein synthesis
Cardiovascular	Increases cardiac muscle mass and increases cardiac output at rest and during maximal exercise
Hematologic	Increases plasma volume and red blood cell mass
Skeletal tissue	Increases bone mineral density and bone turnover
Connective tissue	Increases collagen turnover at nonskeletal sites, including tendons
Metabolism	Increases rates of sweating and thermal dispersion during exercise
Endocrine–acute	Increases the uptake and utilization of glucose by muscle; antagonizes the lipolytic effect of catecholamines on adipose tissue
Endocrine–chronic	Reduces glucose utilization, enhances lipolysis, and increases lean body mass

of depression, anxiety, mental fatigue, and decreased self-esteem. Excessive intraabdominal fat is associated with an increased risk of cardiovascular disease, which is the predominant cause of mortality in patients with GH deficiency.

9. Where do we get the GH that is used therapeutically?

Historically, GH was derived from human cadavers; however, modern techniques have allowed for abundant production of biosynthetic GH, which is identical to the endogenous form.

10. Besides availability, what problem was associated with GH derived from human cadavers?

Creutzfeldt-Jakob disease, an uncommon, rapidly progressive, and fatal spongiform encephalopathy, has been reported to result from iatrogenic transmission through human cadaver pituitary tissue. More than 30 young adults who had received human cadaver pituitary products have died of this disease, and at least 60–70 cases of Creutzfeldt-Jakob disease have been identified in recipients.

11. What are some uses of GH approved by the US Food and Drug Administration?

Historically, the only approved indication for GH therapy was treatment of short stature in children with GH deficiency. Currently, GH is also approved for the treatment of short stature that is idiopathic or associated with Turner's syndrome, Prader-Willi syndrome, Noonan's syndrome, and progressive chronic renal insufficiency in children. GH is also approved for treating wasting in patients with acquired immunodeficiency syndrome and for replacement in adults with GH deficiency.

12. What are some other potential uses of GH?

GH use has other potential indications (1) Russell-Silver syndrome, (2) chondrodysplasia in children, (3) steroid-induced growth suppression, (4) short stature associated with myelomeningocele, (5) any severe wasting state (e.g., wounds, burns, cancer), (6) normal aging, (7) non–islet cell tumor hypoglycemia, (8) gonadal dysgenesis, (9) Down's syndrome, (10) short stature associated with neurofibromatosis, (11) human immunodeficiency virus (HIV)–associated adipose redistribution syndrome (12), and osteoporosis.

13. How does GH help adults with GH deficiency?

The reported beneficial effects in adults with GH deficiency are an increase in muscle mass and function, reduction of total body fat mass, increased plasma volume, and improved peripheral blood flow. Reductions in serum total and low-density lipoprotein cholesterol, reduction in diastolic blood pressure, a trend toward reduction in systolic blood pressure, and beneficial effects on bone metabolism and skeletal mass have also been documented. In addition, improvement in psychological well-being and quality of life can occur with GH replacement.

14. How is GH administered?

GH is administered through subcutaneous injection. In children, the dose can be divided into regimens of two or three times weekly or daily. Daily injections appear to result in greater growth velocity compared with less frequent administration. In adults with GH deficiency, replacement is usually given daily.

15. Why is GH used as an ergogenic aid by athletes?

Some athletes have used GH in an effort to improve performance. Supraphysiologic doses of GH have been reported to increase lean body mass and reduce body fat in trained athletes. In 2010, a clinical research facility in Sydney, Australia, performed the largest randomized control trial to date to determine the effect of GH on body composition and measures of performance. The study showed that GH in both men and women significantly reduced body fat mass, increased lean body mass, and improved sprint capacity but not strength, power, or endurance. The effects were even greater when GH was co-administered with testosterone.

16. What recent developments have been made in testing for GH abuse?

Before 2004, there was no reliable method to detect exogenous GH administration due to difficulties in distinguishing it from endogenous hormones. After years of study and international collaboration, scientists developed a test that has been endorsed by the World Anti-Doping Association. In February 2010, the test caught its first doper, a British rugby player, who was banned from competition for 2 years for the infraction. The test was used experimentally in 2004 and became widely available by 2010, with expanded testing starting during the 2012 Olympic Games. The test's limitations include the need for a blood sample and its inability to detect use >1–2 days before testing.

17. Why was GH abuse so difficult to detect in the past?

GH abuse was difficult to detect in the past because exogenously administered GH is identical in structure to endogenous hormone, so simply detecting GH on a blood sample was not evidence of doping. Additionally, endogenous GH is secreted in a pulsatile manner; therefore, an increased level detected on random testing could simply reflect a natural peak because GH secretion is stimulated by acute exercise. Cadaveric GH has also been used for doping purposes and is difficult to detect because of the normal ratios of GH isomers.

18. How can GH abuse in athletes be detected?

GH doping can be detected by two distinct methods. The first method measures the ratio of the two isoforms of GH, and the second method measures the markers of GH action, such as IGF-1 and propeptide of type III procollagen.

19. How prevalent is GH use among athletes?

The prevalence is not known, but it is thought to be widespread. GH use is probably not as extensive as that of anabolic–androgenic steroids. One limiting factor is the expense. Even a 1-month supply may cost several thousand dollars, depending on dosages.

20. What are the adverse effects of the therapeutic use of GH in adults?

Fluid retention causing edema and carpal tunnel syndrome are common in adults but not in children. Arthralgias, myalgias, paresthesias, and worsening glucose tolerance are also common and may be present in up to one-third of patients taking GH. Other potential side effects include gynecomastia, pancreatitis, behavioral changes, worsening of neurofibromatosis, scoliosis and kyphosis, and hypertrophy of tonsils and adenoids.

21. What are the adverse effects of GH in children?

Intracranial hypertension has been reported in children; this is most common in children with renal disease, although it has also been observed in children with GH deficiency and in girls with Turner's syndrome. GH therapy is associated with an increased risk of slipped capital femoral epiphysis in the same three groups of children. Children with GH deficiency caused by deletion of the GdH gene may develop antibodies to GH with secondary growth deceleration. This phenomenon is rare in other children.

22. What adverse effects occur in athletes using GH?

Little is known about the side effects of GH use in athletes. Chronic abuse of supraphysiologic GH doses may lead to features of acromegaly; osteoarthritis; irreversible bone and joint deformities; increased vascular, respiratory, and cardiac abnormalities; hypertrophy of other organs; hypogonadism; diabetes mellitus; abnormal lipid metabolism; increased risk of breast and colon cancers; and muscle weakness caused by myopathy. Use of GH in combination with anabolic–androgenic steroids may increase left ventricular mass and cause cardiac remodeling.

23. Can GH reverse the natural aging process?

No. However, alternative medicine companies promote products alleged to stimulate increased production of GH in hopes of reversing normal aging. This theory has been sustained partly by a study that suggested that diminished secretion of GH is responsible for the effects of aging, including increased adipose tissue, decreased lean body mass, and thinning of the skin. Although GH replacement has a role in individuals with GH deficiency, no studies have shown that supplemental GH can reverse physiologic aging.

KEY POINTS

- GH secretion is stimulated by exercise, sleep, stress, trauma, and signaling by GH-RH and ghrelin. Inhibition occurs by feedback from somatostatin and insulin-like growth factor-1 (IGF-1).
- GH abuse is thought to be prevalent in athletes to enhance performance, but little evidence supports meaningful performance enhancement, except for some increase in anaerobic exercise capacity.
- Large-scale detection of GH doping has recently become possible, including at the Olympic Games. Current testing relies on either altered GH isoform ratios or altered markers of GH action.
- Long-term effects of supratherapeutic doses of GH in athletes are not known, but there is concern about multiple possible negative effects.

WEBSITES

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CHAPTER 33

Primary Aldosteronism

John J. Orrego

1. Define primary aldosteronism (PA).

PA, first recognized by Jerome Conn in 1954, refers to a group of adrenal disorders characterized by chronic and dysregulated aldosterone excess and mineralocorticoid receptor (MR) activation that occurs despite suppression of renin and angiotensin II and serum potassium concentrations (the major physiologic regulators of aldosterone production), and is nonsuppressible by sodium loading and volume expansion. Adrenocorticotropic hormone (ACTH) and serotonin are acute regulators of aldosterone synthesis.

2. What are the most common subtypes of PA?

- Idiopathic hyperaldosteronism (IHA)—bilateral hyperplasia of the zona glomerulosa
- Aldosterone–producing adenoma (APA) and carcinoma
- Primary adrenal hyperplasia (PAH)—unilateral hyperplasia of the zona glomerulosa
- Familial hyperaldosteronism (FA)

3. How common is PA?

The most common manifestation of excess aldosterone secretion is hypertension. Cross-sectional and prospective studies around the world have substantiated that 5–13% of patients with hypertension, both in general and in specialty clinics, have PA.

4. What are the clinical manifestations of PA?

Aldosterone normally acts at the renal distal convoluted tubule to stimulate the reabsorption of sodium ions (Na^+), as well as secretion of potassium (K^+) and hydrogen ions (H^+), and at the cortical and medullary collecting ducts to cause direct secretion of H^+. In PA, the excess of aldosterone secretion and MR activation in the principal cells results in inappropriate sodium reabsorption via epithelial sodium channels (ENaC) along with increased excretion of potassium through renal outer medullary potassium channels (ROMK), and in the alpha-intercalated cells results in heightened excretion of acid via H^+-ATPase and H^+/K^+-ATPase pumps. All these changes lead to the expansion of intracellular and extracellular volume, left shift in the pressure–natriuresis relationship, hypertension, glomerular hyperfiltration, hypokalemia, and metabolic alkalosis.

In general, patients with APA have more severe hypertension and hypokalemia compared with their IHA counterparts. Although resistant hypertension is common in patients with PA, malignant hypertension is rare. Spontaneous hypokalemia is nowadays an uncommon presenting manifestation of PA. Symptoms are usually those associated with hypertension (headaches and dizziness) or with hypokalemia (muscle weakness and cramping, paresthesias, palpitations, polyuria, and polydipsia).

5. Is hypokalemia a sine qua non for PA?

No. Different series have documented hypokalemia in only 9–37% of patients with PA. In a large single study, almost 50% of patients with APA had hypokalemia, whereas only 17% of those with IHA did. Therefore, normokalemic hypertension is the most common presentation of PA.

6. What is the differential diagnosis of mineralocorticoid hypertension?

Hypertension with hypokalemia and plasma renin suppression is known as *mineralocorticoid hypertension*. The most common cause of mineralocorticoid hypertension is PA. The plasma aldosterone concentration (PAC) is always elevated in PA, whereas all the other types of mineralocorticoid hypertension are characterized by suppressed PAC because of activation of the mineralocorticoid receptor by other compounds or from constitutive activation of collecting tubule sodium channels:

1. Deoxycorticosterone (a precursor of aldosterone with mineralocorticoid activity):
   - Congenital adrenal hyperplasia, caused by 11beta-hydroxylase deficiency and 17alpha-hydroxylase deficiency
   - Deoxycorticosterone-secreting adrenocortical tumors
   - Glucocorticoid-receptor resistance (glucocorticoid receptor mutations, mifepristone)
2. Cortisol (severe hypercortisolemia overwhelms renal 11 beta-hydroxysteroid dehydrogenase type 2 and results in spillover to the mineralocorticoid receptor):
   - Apparent mineralocorticoid excess (AME)
   - Licorice and carbenoxolone ingestion
   - Ectopic ACTH syndrome
3. Mutations in genes that encode the beta and delta subunits of the collecting tubule sodium channels preventing their removal from the cell surface:
   - Liddle's syndrome

7. Why is it important to detect PA?

The primary reason is that hypertension accompanying PA is potentially curable. The most important reason, however, is that patients with PA have a higher prevalence of cardiovascular morbidity and mortality compared with age- and gender-matched patients with primary hypertension and the same degree of blood pressure elevation. Specifically, patients with PA, compared with those with primary hypertension, have increased left ventricular mass and decreased left ventricular function and a higher risk of atrial fibrillation, stroke, and myocardial infarction. They are also more likely to have type 2 diabetes mellitus and metabolic syndrome, increased glomerular filtration rate and renal perfusion pressure, proteinuria, and impaired physical and mental quality of life. These effects seem to be mediated through the activation of mineralocorticoid receptors in the heart and blood vessels, with subsequent impairment of endothelial function. Therefore, timely detection and treatment (surgery or mineralocorticoid receptor antagonists) can reduce the impact of aldosterone on these tissues.

8. Which patients with hypertension should be investigated for PA?

Testing for PA should be considered in patients with any of the following:

- Adrenal incidentaloma and hypertension
- Hypertension and hypokalemia
- Severe hypertension (systolic BP >150 mm Hg or diastolic BP >100 mm Hg)
- Resistant hypertension (uncontrolled BP on ≥3 antihypertensive medications)
- Hypertension and family history of hypertension or cerebrovascular disease at age <40 years old
- All hypertensive first-degree relatives of patients with PA
- Hypertension and sleep apnea

9. What tests are recommended to detect possible cases of PA (case detection)?

Current screening for PA relies on simultaneous measurement of plasma aldosterone and plasma renin levels, which allow calculation of the aldosterone-to-renin ratio (ARR). Plasma renin activity (PRA) has traditionally been used to calculate the ARR; however, measurement of direct renin concentration (DRC) has become increasingly popular because the assay procedure is less labor and time intensive and is cheaper and more widely available. If possible, plasma aldosterone concentration (PAC) and PRA or DRC samples should be collected in the morning, with the patient out of bed for at least 2 hours and seated for 5–15 minutes. Preparation before ARR testing includes correction of hypokalemia (as hypokalemia reduces aldosterone secretion), sodium-unrestricted diet, and withdrawal of mineralocorticoid receptor antagonists (steroidal and nonsteroidal), renin inhibitors, and amiloride (if >5 mg per day) 4–6 weeks before testing, if clinically feasible.

The first step is to document a suppressed PRA (<1 ng/mL/hr) or DRC (<lower limit of normal in pg/mL) in the context of an inappropriately high plasma aldosterone concentration (PAC) (>10–15 ng/dL). The second step is to divide the PAC by the PRA or DRC to calculate the ARR. An ARR >20 strongly suggests PA.

10. What medications affect the ARR?

Since no other condition aside from PA can cause an elevated PAC in the setting of a frankly suppressed renin, medications do not cause false-positive ARR results. Therefore, when suspicion is high that a patient has PA, screening can be done no matter what medications the patient is taking; if the diagnostic criteria are met, screening does not need to be repeated off medications. However, medications can cause false-negative results, either by raising the PRA or DRC (most often) or suppressing the PAC. Thus, if testing is borderline or negative and PA is still suspected, medications may need to be discontinued and the tests repeated.

These are the most common medications that cause false-negative test results:

- Mineralocorticoid receptor antagonists, renin inhibitors, and high-dose amiloride can all elevate the PRA or DRC, causing a falsely negative ARR. If discontinuation of these is indicated, they should be stopped 4–6 weeks before ARR testing. When this is not safe, PA-related testing can still be pursued; if the PRA or DRC level is suppressed on these medications, the test is valid.
- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and diuretics can also sometimes elevate the PRA or DRC and cause a false-negative ARR. Thus, in cases where the ARR is borderline or negative but PA is still suspected, these medications should be discontinued briefly (1–2 weeks) and testing repeated. However, if the PRA or DRC levels are suppressed, these medications will not produce false results.
- Beta-adrenergic receptor blockers and central alpha-2 agonists (clonidine, alpha-methyldopa) suppress PRA or DRC and, to a lesser degree, PAC in individuals with normal levels; therefore, although ARR may increase modestly in hypertensive patients without PA treated with these medications, PAC remains <15 ng/dL and test interpretation is not usually affected.
- Calcium-channel blockers belonging to the dihydropyridine family can elevate the PRA or DRC and slightly decrease PAC, also causing a false-negative ARR.
- Verapamil slow-release, hydralazine, prazosin, doxazosin, and terazosin have little effect on the ARR and may be substituted, if needed, for temporary blood pressure control during case finding and confirmatory testing.

11. What tests are recommended to confirm PA (case confirmation)?

Since nothing else besides PA can cause renin suppression in the context of hyperaldosteronism, confirmatory testing is not considered necessary when all three of the following criteria are met:

- Spontaneous hypokalemia
- PRA or DRC suppressed
- PAC >20 ng/dL

Otherwise, inappropriate aldosterone secretion must be demonstrated with one of these maneuvers:

- *Oral sodium loading test*: Intravascular volume expansion should normally suppress aldosterone secretion. In the oral sodium loading test, the patient consumes >200 mmol (6 g) of dietary sodium for 3 days, and 24-hour urine samples for aldosterone, sodium, and creatinine are collected from day 3 through day 4. Urinary excretion of aldosterone (high-performance liquid chromatography [HPLC]–tandem mass spectrometry) >12 mcg/day confirms a diagnosis of PA. Urinary sodium of at least 200 mmol/day ensures the adequacy of the test. Hypertension and hypokalemia should be controlled before this test is performed.
- *Saline infusion test*: An alternative test is acute volume expansion by administering 2 liters of normal saline intravenously over 4 hours while the patient stays in the recumbent position, with measurement of PAC at baseline and at the end of the saline infusion. Post-infusion PAC >10 ng/dL confirms the diagnosis. PAC <5 ng/dL rules out PA, and levels between 5 and 10 ng/dL are indeterminate; another confirmatory test may be considered.

12. Are any other tests used for case confirmation?

Additional testing to confirm the diagnosis is seldom necessary. Less commonly used confirmatory tests in the United States include the captopril challenge test and the fludrocortisone suppression test. In the former, the patient receives 25–50 mg of captopril orally after sitting or standing for at least 1 hour. Blood is drawn 2 hours later while the patient is seated. PAC is normally suppressed by >30% by captopril. In patients with PA, PAC remains elevated, and PRA or DRC remains suppressed. In the latter test, the patient takes 0.1 mg of fludrocortisone and slow-release potassium chloride (KCl) supplements orally every 6 hours and a high-sodium diet for 4 days. Upright PAC >6 ng/dL at 10 a.m., on day 4, confirms PA, provided PRA is <1 ng/mL/h and cortisol is lower than the value obtained at 7:00 a.m.

13. What should be the initial imaging study once PA is confirmed (subtype classification)?

High-resolution adrenal computed tomography (CT) is the recommended initial study to determine the subtype (adenoma versus hyperplasia) and exclude adrenal carcinoma once a diagnosis of PA is confirmed. Magnetic resonance imaging (MRI) has no advantage over CT in subtype evaluation of PA, not only because MRI has less spatial resolution than CT but also because it is more expensive, and the scan time is longer. If the patient is interested in surgery (if unilateral disease is proven), bilateral adrenal vein sampling (AVS) by an experienced interventional radiologist is the next step, regardless of the results of cross-sectional imaging (normal-appearing glands, unilateral or bilateral adrenal limb thickening, or micro- or macroadenomas).

14. What is the most common form of PA?

IHA is the most common form of PA, accounting for 60–70% of cases in most series. IHA is characterized by bilateral hyperplasia (diffuse and focal) of the zona glomerulosa layer of both adrenal glands. Although the cause has not yet been determined, it has been hypothesized that there is supranormal sensitivity of the zona glomerulosa to physiologic concentrations of angiotensin II in affected adrenal glands. However, the hyperaldosteronism in these patients is not reversed with angiotensin II inhibitors. IHA is generally a milder disease with less aldosterone hypersecretion and, therefore, milder hypertension and mild or no hypokalemia.

15. What is the second most common cause of PA?

APAs comprise 30–40% of PA cases. Patients with APA are usually younger (<50 years) and have higher PACs, resulting in more severe hypertension and hypokalemia. APAs are small (<2 cm), occur more commonly in the left adrenal gland, and are composed of zona glomerulosa cells, zona reticularis cells, and hybrid cells with characteristics of both layers. APAs are also known as Conn's syndrome.

16. What other features differ between APAs and IHA?

APAs produce greater amounts of aldosterone compared with IHA and other forms of PA; consequently, the degree of hypertension and biochemical abnormalities (hypokalemia and PAC levels) tend to be more severe in patients with an APA. APAs also demonstrate partial responses to ACTH stimulation, whereas the adrenal glands in IHA remain primarily under the control of angiotensin II. PAC in patients with APAs, therefore, parallels the normal circadian rhythm of ACTH secretion (highest in the AM and lowest in the PM), whereas PAC in patients with IHA does not show diurnal variation but increases with upright posture. This is the basis for the (seldom used) posture test in which PAC levels are drawn at baseline in the morning and after 4 hours of upright posture; during this test, PAC decreases in patients with an APA and increases in patients with IHA.

17. What is PAH?

This is an uncommon cause of PA characterized by unilateral micronodular or macronodular hyperplasia of the zona glomerulosa layer. The clinical presentation and outcome of these patients are similar to those with APAs. The treatment is laparoscopic adrenalectomy of the affected gland.

18. Why is AVS the gold-standard test for subtype classification?

Nonfunctional adrenal incidentalomas are common, true APAs may be very small, and the adrenal enlargement seen in IHA can be asymmetric. For these reasons, adrenal imaging alone can lead to significant diagnostic errors and unnecessary surgery. In most cases, therefore, when surgical cure is being considered, AVS is a fundamental diagnostic step to accurately differentiate between unilateral and bilateral adrenal hyperaldosteronism. In a large series of patients with PA who underwent AVS at the Mayo Clinic, the CT scan was accurate in only 53% of patients. Based on CT findings, 22% of patients would have been incorrectly excluded as candidates for adrenalectomy, and 25% might have had unnecessary or inappropriate surgery.

19. How is AVS performed?

A sampling catheter is introduced in either the left or right femoral vein for sampling the left and right adrenal veins and the inferior vena cava (IVC). Plasma aldosterone and serum cortisol levels are obtained from these sites at baseline and following a continuous cosyntropin (synthetic ACTH) infusion. Cortisol levels are obtained to ensure that the adrenal veins are properly catheterized; the adrenal vein—to—IVC cortisol ratio is typically >10:1. Dividing the right and left adrenal vein aldosterone levels by their respective cortisol level corrects for the dilutional effect of the inferior phrenic vein flow into the left adrenal vein (cortisol-corrected ratios). APAs produce large amounts of aldosterone; the normal adrenal vein aldosterone level is 100–400 ng/dL, whereas APAs may generate concentrations of 1000–10,000 ng/dL. A cortisol-corrected aldosterone ratio from the high side to the low side >4:1 is indicative of unilateral aldosterone hypersecretion.

20. Why should adrenal venous sampling be performed by an experienced interventional radiologist?

Collection of blood for measurement of aldosterone and cortisol from the left adrenal gland is relatively simple because the venous effluent drains directly into the left renal vein. The venous flow from the right adrenal, however, flows directly into the IVC. Catheterization of the right adrenal vein is more difficult because of its smaller size and greater angulation compared with the contralateral vein. The success rate for right adrenal vein catheterization increases from 74% to 96% in experienced hands. Complications such as adrenal hemorrhage and adrenal vein dissection during AVS are less common in expert hands.

21. When is AVS not indicated in patients with documented PA pursuing a surgical cure?

AVS is not considered necessary when all three of the following criteria are met:

- Age <35 years
- Severe PA as manifested by spontaneous hypokalemia and PAC >30
- Unilateral adrenal macroadenoma (>1 cm but <2 cm) on cross-sectional imaging

AVS is also not necessary when the evaluation strongly supports a diagnosis of IHA or if the patient is not otherwise interested in or is unable to undergo surgery.

22. Are there any other diagnostic tests?

If both adrenal veins are not successfully catheterized, a posture stimulation test may be informative in patients with a unilateral adrenal mass. In most patients with APA, the PAC is relatively unaffected by increasing angiotensin II levels upon standing, whereas in most patients with IHA, the hyperplastic zona glomerulosa of both adrenal glands has enhanced sensitivity to angiotensin II. Therefore, PAC levels increase with upright posture in patients with IHA and decrease or remain unchanged in patients with APAs.

Recent advances in functional imaging combined with PET/CT or PET/MRI offer the potential to precisely localize the source of hyperaldosteronism in the affected adrenal gland. These imaging modalities are used in combination with newer adrenocortical radiotracers, including ^{11}C-metomidate (MTO), ^{18}F-CETO, ^{18}F-CDP2230, and CXCR4.

23. What are the different forms of *familial hyperaldosteronism (FH)*?

- FH type I or glucocorticoid-remediable aldosteronism (GRA) due to a *CYP11B1/CYP11B2* chimeric gene.

  Humans possess two mitochondrial 11 beta-hydroxylase isoenzymes responsible for cortisol and aldosterone synthesis (designated CYP11B1 and CYP11B2, respectively). Both are encoded on chromosome 8. CYP11B1, which is responsible for the conversion of 11-deoxycortisol to cortisol, is expressed only in the zona fasciculata. CYP11B2, which is responsible for the conversion of corticosterone to aldosterone, is expressed only in the zona glomerulosa. CYP11B1 activity is stimulated by ACTH, whereas CYP11B2 is stimulated by angiotensin II or hypokalemia.

  GRA results from a heritable mutation that causes the fusion of the promoter (regulatory) region of the *CYP11B1* gene with the structural (coding) region of the *CYP11B2* gene. The resulting chimeric gene product synthesizes aldosterone and its precursors in the zona fasciculata in response to ACTH (instead of angiotensin II). The presentation of GRA is variable, with some patients having normal blood pressure and others manifesting severe and refractory hypertension at a young age. Less than 50% of patients with GRA have spontaneous hypokalemia. Strokes, mainly hemorrhagic, resulting from a ruptured intracranial aneurysm, occur in almost 20% of affected individuals. The metabolites (18-hydroxycortisol and 18-oxocortisol) can serve as biochemical markers that facilitate the identification of affected family members. Excessive aldosterone secretion can usually be inhibited by the administration of glucocorticoids that suppress ACTH secretion by the pituitary.

- FH type II is caused by germline *CLCN2* (encoding the chloride voltage-gated channel 2) pathogenic variants. FH type II is an autosomal dominant disorder characterized by unilateral (APA) or bilateral (IHA) excessive aldosterone secretion, which does not suppress with dexamethasone. Patients with this condition are clinically indistinguishable from those with sporadic PA.
- FH type III is caused by germline *KCNJ5* pathogenic variants. Patients with this condition have severe and refractory hypertension and massive adrenal hyperplasia requiring bilateral adrenalectomy at a young age for uncontrolled hypertension.
- FH type IV is caused by germline *CACNA1H* (encoding the calcium voltage-gated channel subunit alpha1 H) pathogenic variants.
- Primary aldosteronism with seizures and neurologic abnormalities (PASNA) caused by germline CACNA1D pathogenic variants.

24. What patients with PA should be treated medically?

Medical therapy, along with a daily sodium intake of ≤1.5 grams as recommended by the American Heart Association for patients with hypertension, should be the first-line treatment for patients with nonlateralizing PA or for those with no access to reliable AVS, inconclusive AVS results, or when adrenalectomy is contraindicated, unfeasible, or declined by the patient. Patients with an APA who are planning surgery should also be treated medically before their surgery. Treatment goals are normalization of serum potassium without the need for potassium supplementation, blood pressure control with a reduced number of antihypertensive medications, and de-suppression and maintenance of the PRA or DRC within the normal range.

25. What medications are used to treat PA?

The medications of choice are spironolactone and eplerenone, which are steroidal mineralocorticoid receptor antagonists (MRA). Spironolactone is a nonselective derivative of progesterone that competitively antagonizes the MR. Eplerenone is a competitive and selective MR antagonist that has 50% of the potency of spironolactone. Spironolactone doses are usually 25–200 mg per day; eplerenone doses are usually 25–50 mg twice daily. However, higher doses are often required. MRA doses should be titrated up until blood pressure is controlled, serum potassium levels are normal without the need for potassium supplements, and PRA is in the 0.7–2.0 ng/mL/hour or DRC in the 10–20 mU/L range. Hypokalemia is corrected immediately, whereas hypertension responds after 4–8 weeks.

Because spironolactone interferes with the action of androgens, side effects can include decreased libido, impotence, nipple tenderness, and gynecomastia in men and menstrual irregularities in women. Eplerenone is more expensive but does not have many of the side effects seen with spironolactone. To avoid the dose–related side effects of spironolactone and reduce the cost of using eplerenone, some providers use a combination of lower doses of the two medications. If blood pressure is not controlled with adequate doses of an MRA, additional blood pressure medications should be added. In patients who are intolerant to MRAs, amiloride (5–15 mg twice daily), an epithelial sodium channel antagonist, corrects hypokalemia within several days. A concomitant antihypertensive agent is usually necessary to reduce blood pressure. Success also has been reported in IHA treated with calcium channel blockers (calcium is involved in the final common pathway for aldosterone production) and ACE inhibitors (IHA appears to be sensitive to low concentrations of angiotensin II). Promissory nonsteroidal MRAs (finerenone) and aldosterone synthase inhibitors (baxdrostat) are currently being evaluated in patients with PA.

26. What patients with PA should be referred to surgery?

Unilateral laparoscopic adrenalectomy is the procedure of choice for patients with benign unilateral hyperaldosteronism. Fifty percent of patients with APA can stop their blood pressure medications postoperatively, and the other half achieve better blood pressure control with a reduced number of blood pressure medications. Nearly all patients remain normokalemic after MRAs are discontinued following successful adrenalectomy. The following three groups of patients should be referred for surgery:

- Patients with unequivocal lateralization of aldosterone hypersecretion on AVS
- Hypertensive patients <35 years of age with spontaneous hypokalemia, PAC >30 ng/dL, and a unilateral adrenal macroadenoma (1–2 cm) with normal contralateral adrenal morphology (AVS is not needed in this subgroup)
- Patients with aldosterone-producing adrenocortical carcinoma (open adrenalectomy)

27. Why is the International Histopathology Consensus for Unilateral Primary Aldosteronism (HISTALDO) useful?

Because it helps standardize nomenclature and achieve consistency among pathologists for the histopathologic diagnosis of unilateral PA. CYP11B2 immunohistochemistry should be incorporated into the routine clinical diagnostic workup to localize the likely source of aldosterone production.

Based on histopathological findings, the following categories were established:

- Aldosterone-producing adrenocortical carcinoma (APACC).
- APA: well-circumscribed CYP11B2-positive solitary neoplasm (≥10 mm diameter) composed of clear or compact eosinophilic cells or both cell types.
- Aldosterone-producing nodule (APN): CYP11B2-positive lesion (<10 mm diameter) morphologically visible with hematoxylin-eosin staining.
- Aldosterone-producing micronodule (APM), formally known as aldosterone-producing cell cluster: CYP11B2-positive lesion (<10 mm diameter) composed of zona glomerulosa cells located beneath adrenal capsule that do not differ in morphology from adjacent adrenocortical cells by hematoxylin-eosin staining.
- Multiple aldosterone-producing nodules (MAPN) or multiple aldosterone-producing micronodules (MAPM), formally known as micronodular hyperplasia: Multiple APN or multiple APM located beneath the adrenal capsule with intermittent regions of normal zona glomerulosa.
- Aldosterone-producing diffuse hyperplasia (APDH): a relatively broad and uninterrupted strip of zona glomerulosa cells with more than half of these cells displaying CYP11B2-positive immunostaining.

28. How should medications for PA be managed in the postoperative period?

The following are general guidelines for postoperative management after successful surgical removal of an APA:

- Reduce all blood pressure medications by 50%.
- Stop all medications that can cause hyperkalemia: spironolactone, eplerenone, ACE inhibitors, ARBs, and potassium supplements.
- Monitor blood pressure daily.
- Check serum potassium weekly for 4 weeks.
- Start fludrocortisone if serum K >5.2 mEq/L.

29. Are there any somatic mutations associated with adrenal-producing adenomas?

Next-generation sequencing (NGS) enabled the identification of somatic mutations that cause inappropriate aldosterone production in patients with PA. The affected genes described so far include the aldosterone-driving genes *KCNJ5* (encoding the Kir 3.4 K^+ channel), *ATP1A1* (encoding a Na^+/K^+ ATPase alpha subunit), *ATP2B3* (encoding a Ca^{2+} ATPase), and *CACNA1D* (encoding the calcium voltage-gated channel subunit alpha1 D).

A meta-analysis that included 13 studies that recruited 1636 patients (age 49 ± 4 years; 55% females) found that the overall prevalence of KCNJ5 mutations was 43% (range = 12–80%). Their rate was lower in the studies done in Europe, the United States, and

Australia (35%) than in Japan and China (63%). Compared with the wild type, the mutated APA patients were younger, had higher plasma aldosterone, and were more often females (67% versus 44%).

In aldosterone-producing cells of the zona glomerulosa, the Kir 3.4 K^+ channel is highly expressed and plays a key role in maintaining cell membrane hyperpolarization. Mutations in the KCNJ5 gene were found to impair the selectivity of the filter for K^+ and to allow Na^+ influx, leading to zona glomerulosa cell membrane depolarization, the opening of T-type Ca^{2+} channels, and activation of the Na^+/Ca^{2+} exchanger; the ensuing Ca^{2+} influx activates aldosterone synthesis and secretion.

Somatic heterozygous *KCNJ5* mutations were present in 180 (38%) of 474 unselected patients with APA collected through the European Network for the Study of Adrenal Tumors, whereas *CACNA1D* mutations were identified in 44 (9.3%), *ATP1A1* mutations in 25 (5.3%), and *ATP2B3* mutations in 8 (1.7%) of APAs.

When using an aldosterone synthase (CYP11B2) immunohistochemistry (IHC)–guided (enabling the identification of aldosterone-producing cells) next-generation sequencing (NGS) approach, the prevalence of somatic mutations in APAs is higher (88% in White Americans and 89% in Blacks) than in previous studies using conventional approaches.

KEY POINTS: PRIMARY ALDOSTERONISM

- Spontaneous hypokalemia in a hypertensive patient should suggest the possibility of primary aldosteronism (PA)—but normokalemic hypertension is the most common presentation.
- PA is usually caused by bilateral adrenal hyperplasia or a small adrenal adenoma.
- The best test for PA case detection is the combination of a suppressed PRA (<1 ng/mL/hr) or DRC (<lower limit of normal in pg/mL), a high plasma aldosterone concentration (PAC) (>10–15 ng/dL), and an ARR >20.
- PA is confirmed with a 24-hour urine aldosterone >12 mcg/day after salt loading.
- Because computed tomography and magnetic resonance imaging are often unable to distinguish adenomas from hyperplasia, adrenal venous sampling is often necessary to determine whether the excessive aldosterone secretion is unilateral or bilateral.
- Adenomas are treated surgically; bilateral hyperplasia is treated pharmacologically with aldosterone receptor antagonists (spironolactone and/or eplerenone).
- Glucocorticoid-remediable aldosteronism is treated with physiologic doses of glucocorticoids.

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Pheochromocytomas and Paragangliomas

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CHAPTER 34

1. What are pheochromocytomas and paragangliomas?

Pheochromocytomas and paragangliomas are tumors of the autonomic nervous system. A pheochromocytoma (PCC) is an adrenal medullary tumor that arises from chromaffin cells and can secrete metanephrines and catecholamines.

A paraganglioma (PGL) is an extra-adrenal tumor derived from sympathetic or parasympathetic ganglia. Sympathetic PGLs can secrete metanephrines and catecholamines. Head and neck PGLs (HNPGLs) are typically parasympathetic and are nonsecreting. About 4% of HNPGLs are secretory.

Overall, about 80% of these tumors are PCC and 20% are PGLs.

2. How common are pheochromocytoma and paraganglioma?

The incidence of PCC and PGL is 0.66 cases per 100,000 people per year (7 people per year in a city of 1 million population). PCC and PGL account for 0.2–0.6% of patients with hypertension in general outpatient clinics. Autopsy studies reveal undiagnosed tumors in at least 0.05% of people, indicating that many PCCs and PGLs go undiagnosed. PCC accounts for about 1–5% of adrenal incidentalomas.

3. Where are paragangliomas located?

PGLs can occur anywhere from the skull base to the pelvic floor. Most PGLs arise in the abdomen and pelvis, often at the junction of the vena cava and the left renal vein, or at the organ of Zuckerkandl, which resides at the aortic bifurcation near the branching of the inferior mesenteric artery. PGLs also develop in the thorax, including the pericardium, the bladder, and the prostate gland. HNPGLs are most commonly found near the carotid body but can form anywhere in the neck or skull base.

4. How are genetics important in pheochromocytoma and paraganglioma?

Around 30 –40% of patients with PCC and PGL carry an inherited germline pathogenic variant (mutation) in one of over 12 well-characterized susceptibility genes (see Table 34.1). Germline pathogenic variants in these genes are inherited in an autosomal dominant pattern, with variable penetrance depending on the gene. Given the high heritability of PCC/PGL, genetic testing is recommended for all patients who have PCC or PGL.

5. Is parent of origin relevant to any of the pheochromocytoma-paraganglioma syndromes?

Yes! Hereditary PGL/PCC syndromes that arise from *Succinate Dehydrogenase Subunit D* (*SDHD*) germline pathogenic variants are paternally inherited. This means that the syndrome is only clinically relevant if the *SDHD* pathogenic variant is inherited from the proband's father. Offspring who inherit an *SDHD* pathogenic variant from their mother can still pass it to their children, but they do not exhibit the clinical phenotype for hereditary PCC/PGL syndrome. It is important to note that male offspring who inherit the *SDHD* pathogenic variant from their mother can have clinically affected sons and daughters. *Succinate Dehydrogenase Assembly Factor 2 (SDHAF2)* pathogenic variant inheritance has a similar parent-of-origin effect.

6. How do *SDHx* germline pathogenic variants lead to pheochromocytoma and paraganglioma?

Succinate Dehydrogenase, also referred to as Complex II in the electron transport chain, is an enzyme found on the mitochondrial membrane that plays a role in oxidative phosphorylation and the citric acid cycle. It is made up of four subunits with specific roles. SDHA and SDHB

TABLE 34.1 Features of Syndromes Associated With Pheochromocytoma and Paraganglioma

GENE	SYNDROME	PREVALENCE OF GENETIC CHANGE IN PCC/PGL	PENETRANCE FOR PCC/PGL	METASTATIC PCC/PGL RISK	SOME CLINICAL FEATURES OF ASSOCIATED SYNDROME
RET	MEN2A & MEN2B	6%	50%	<5%	MTC PCC (often bilateral) Hyperparathyroidism (MEN2A) (See MEN Chapter for details)
NF1	Neurofibromatosis type 1	3%	8–14%	12%	Neurofibromas (plexiform and/or cutaneous) PCC (often bilateral) Café-au-lait spots Lisch nodules Optic gliomas Long bone dysplasia
VHL	Von Hippel-Lindau	4–7%	20%	<5%	PCC >PGL (PCC often bilateral) CNS hemangioblastoma Endolymphatic sac tumors Pancreatic cysts & PNETs RCC & renal cysts
SDHA	Hereditary PGL/PCC Syndrome	<1–3%	10% by age 70	12%	PCC & PGL GIST RCC
SDHB	Hereditary PGL/PCC Syndrome	9–10%	22–26% by age 60	25–50%	PCC & PGL RCC GIST
SDHC	Hereditary PGL/PCC Syndrome	1%	25% by age 60	<5%	Head-neck & thoracic PGL PCC RCC GIST
SDHD	Hereditary PGL/PCC Syndrome	2–9%	43% by age 60	3–8%	Head-neck PGL Multifocal primary PCC/PGL RCC GIST paternal inheritance pattern
SDHAF2	Hereditary PGL/PCC Syndrome	<1%	Unknown	Unknown but low	Head and neck PGL RCC GIST paternal inheritance pattern

PCC, Pheochromocytom; *PGL*, paraganglioma; *MEN*, multiple endocrine neoplasia, *RET,* Rearranged during Transfection; *NF1,* Neurofibromatosis type 1; *VHL,* Von Hippel-Lindau*; SHDA*, Succinate Dehydrogenase Subunit A; *SDHB,* Succinate Dehydrogenase Subunit B*; SDHC,* Succinate Dehydrogenase Subunit C*; SDHD,* Succinate Dehydrogenase Subunit D; *CNS*, central nervous system; *PNET*, pancreatic neuroendocrine tumor; *RCC*, renal cell carcinoma; *GIST*, gastrointestinal stromal tumor.

Adapted from Sharma S, Fishbein L. Diagnosis and management of pheochromocytomas and paragangliomas: a guide for the clinician. *Endocr Pract*. 2023;29(12):999–1006; Turin CG, Crenshaw MM, Fishbein L. Pheochromocytoma and paraganglioma: germline genetics and hereditary syndromes. Endocr Oncol. 2022;2(1):R65–R77.

bind to substrates and catalyze enzymatic reactions. SDHC and SDHD anchor the complex to the mitochondrial membrane. A fifth protein, Succinate Dehydrogenase Assembly Factor 2 (SDHAF2), helps stabilize the overall complex and assists in catalyzing enzymatic reactions. Specifically, Succinate Dehydrogenase oxidizes succinate to fumarate as well as reducing flavine adenine dinucleotide (FAD) to FADH.

Pathogenic variants in the genes encoding the subunits lead to a dysfunctional complex and cause accumulation of succinate, which leads to decreased DNA and histone demethylation and subsequent stabilization of hypoxia-inducible factors (HIFs). This pseudohypoxic state with elevated HIF activity leads to increased expression of genes for glycolysis, cell survival, cell proliferation, and angiogenesis.

7. No longer the ‘rule of 10’ for pheochromocytomas and paragangliomas?

This rule was previously used to describe the characteristics of PCCs: 10% are extra-adrenal (PGLs), 10% are multiple or bilateral, 10% are malignant, 10% occur in children, and 10% are familial. More recent data suggest this is no loner true. 15-20% of PCCs/PGLs are extra-adrenal. PCCs/PGLs are no longer considered to be “benign” or “malignant”; rather, the WHO prefers to call them either “localized” or “metastatic” as all PCC/PGL have the potential to metastasize. 10 –20% of PCC/PGL spread to nonchromaffin tissues and are considered metastatic. Up to 30 –40% of PCCs/PGLs are hereditary. For children, PCCs/PGLs are even more likely to be inherited (up to 80%), bilateral- or extra-adrenal, and metastatic. Thus, the “rule of 10” for PCC/PGL is now obsolete.

8. What do pheochromocytomas and paragangliomas secrete?

PCC/PGL make and secrete norepinephrine (and its metabolite normetanephrine), epinephrine (and its metabolite metanephrine), and/or dopamine. Most PCCs/PGLs secrete norepinephrine. Tumors that also produce epinephrine will be intra-adrenal due to the presence of the enzyme phenylethanolamine N-methyltransferase (PNMT) in the adrenal medulla, which is upregulated by cortisol and converts norepinephrine to epinephrine. Dopamine is most commonly associated with head and neck PGLs (HNPGLs) and also can be seen in metastatic disease.

9. How are catecholamines produced/metabolized, and why is that relevant to understanding pheochromocytoma and paraganglioma?

Catecholamines are synthetized from tyrosine, which is actively transported into chromaffin cells. Tyrosine conversion to DOPA by tyrosine hydroxylase is the rate-limiting step in catecholamine synthesis (Fig. 34.1). The adrenal medulla contains the PNMT enzyme which is upregulated by cortisol from the surrounding adrenal cortex and converts norepinephrine to epinephrine. Therefore, 80% of the secretion from the normal medulla is epinephrine. In PCC/PGL, PNMT is often silenced by hypermethylation; therefore, most PCC/PGL are norepinephrine-predominant. Because extra-adrenal sympathetic ganglia lack the PNMT enzyme, high levels of epinephrine/metanephrine suggest the presence of adrenal PCC.

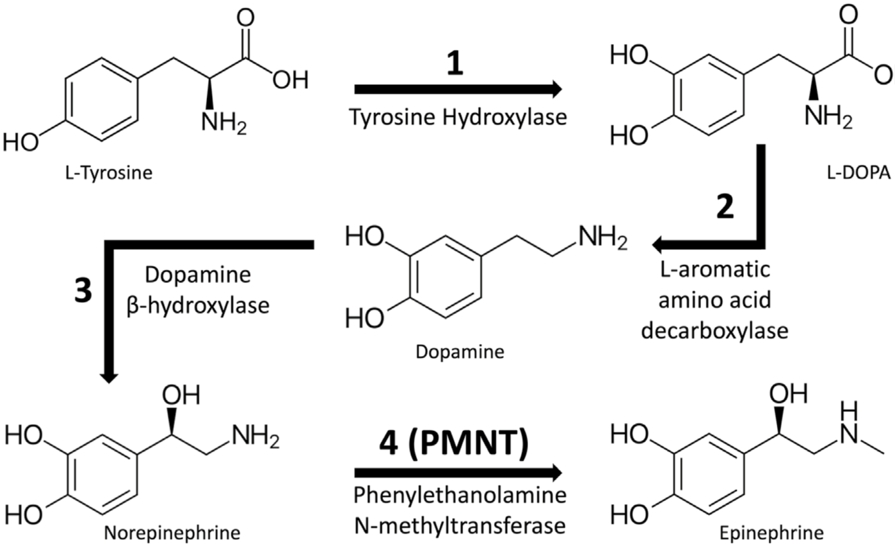

Fig. 34.1 Catecholamine synthesis. *L-DOPA*, Levodopa; *PNMT*, phenylethanolamine N-methyltransferase.

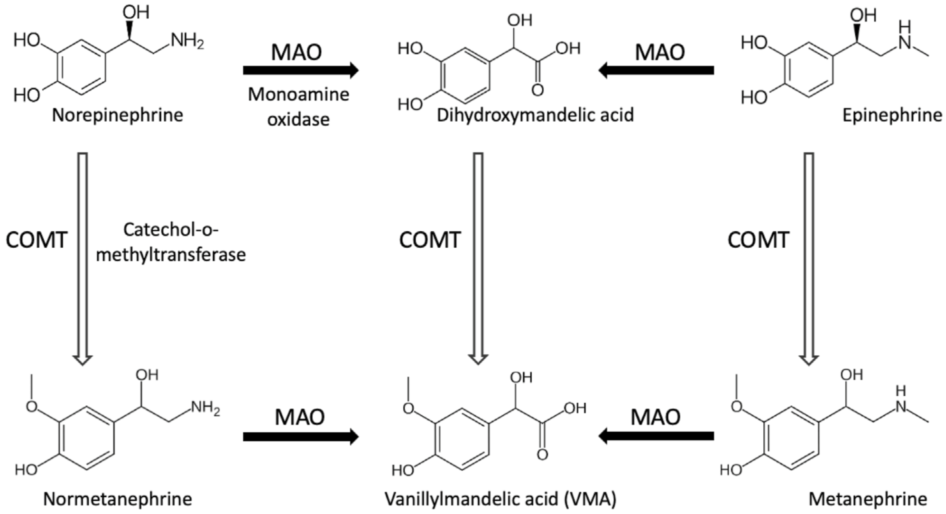

Fig. 34.2 Catecholamine metabolism. *COMT*, Catechol-o-methyltransferase; *MAO*, monoamine oxidase.

Catecholamines are cleared from the circulation by reuptake in sympathetic nerve terminals or metabolism through two enzymatic pathways, followed by sulfate conjugation and renal excretion. See the metabolism pathway below (Fig. 34.2).

10. Describe the adrenergic receptors that bind circulating catecholamines.

There are two types of adrenergic receptors that mediate the physiologic effects of catecholamines: alpha- and beta-adrenergic receptors. Each type has several subtypes:

- Alpha (α)-1 is a postsynaptic receptor that causes vasoconstriction and increases blood pressure when activated.
- Alpha (α)-2 is a presynaptic receptor that, when activated, inhibits norepinephrine secretion and overall reduces central sympathetic tone. This leads to a decrease in blood pressure.
- Beta (β)-1 receptors mediate cardiac effects; stimulation causes positive inotropic and chronotropic effects on the heart, increased renin secretion in the kidney, and lipolysis in adipocytes.
- Beta (β)-2 receptor activation causes bronchodilation, vasodilation in skeletal muscle, glycogenolysis, and increased norepinephrine release from sympathetic nerve endings.
- Beta (β)-3 regulates energy expenditure and lipolysis. Activation of this receptor also causes detrusor muscle relaxation in the bladder.

11. What are common clinical manifestations of catecholamine-secreting tumors?

Sporadic PCCs/PGLs most commonly occur in the fourth to fifth decades of life whereas hereditary cases generally present at younger ages. About 50% of patients with PCC/PGL are asymptomatic. When symptoms are present, they can be episodic or sustained. Hypertension, palpitations, diaphoresis, and headaches may be more common with norepinephrine-secreting PCC/PGL. Other symptoms may include anxiety, hyperglycemia, dyspnea, chest/epigastric pain, nausea, weakness, or tremors. Spells may be spontaneous or precipitated by postural change, exercise, medications, or maneuvers that increase intraabdominal pressure. The classic triad of headaches, diaphoresis, and palpitations is present only in a subset of patients. Although the most common sign of secretory PCC/PGL is sustained or paroxysmal hypertension, some patients are normotensive.

Additional clinical and biochemical manifestations of PCCs/PGLs include orthostatic hypotension (due to hypovolemia and impaired arterial and venous constriction responses), weight loss, constipation (megacolon or functional ileus may be the presenting symptom), Raynaud's phenomenon, leukocytosis, and polycythemia. Hyperglycemia from catecholamine–induced antagonism of insulin release is commonly observed. Given this broad range of clinical manifestations across multiple organ systems, secretory PCCs/PGLs have been known as the "great mimickers."

12. Describe the cardiovascular manifestations of pheochromocytomas and paragangliomas.

Cardiovascular manifestations of PCCs/PGLs include arrhythmia, catecholamine-induced cardiomyopathy, myocardial infarction, and stroke. Although pulmonary edema may result from cardiomyopathy, transient pulmonary vasoconstriction and increased capillary permeability can cause noncardiogenic pulmonary edema as well. Blood pressure can be labile due to episodic catecholamine secretion, chronic hypovolemia, and impaired sympathetic reflexes.

13. Describe the neurological symptoms related to pheochromocytomas and paragangliomas.

Neurologic symptoms are less common but can occur. Seizure, encephalopathy, and cerebral infarction may occur as a result of hypertension, vasoconstriction, intracerebral hemorrhage, or embolization of thrombi. Malignant hypertension with cerebral edema, encephalopathy, or posterior reversible encephalopathy syndrome (PRES) has also been described.

14. What are some of the nonclassical manifestations of pheochromocytomas and paragangliomas?

PCCs/PGLs are a type of neuroendocrine tumor, and therefore the cells have the ability to make and secrete any hormone. Occasionally, PCC/PGL produces corticotropin (ACTH), leading to ectopic Cushing's syndrome with possible hypokalemic alkalosis. In rare instances, production of vasoactive intestinal peptide (VIP) causes severe diarrhea and hypokalemia. Hypercalcemia due to adrenergic stimulation of the parathyroid glands or elaboration of parathyroid hormone–related peptide (PTHrP) can also occur. Lactic acidosis can be seen with catecholamine–associated disturbance in tissue oxygen delivery.

15. Can pheochromocytomas and paragagliomas metastasize?

Yes. About 10 –20% of PCC/PGL can metastasize to tissues without chromaffin cells, such as lymph nodes, brain, and bone. Liver and lung can also have metastatic disease. Of all hereditary PCC/PGL, *SDHB*–associated PCC/PGL have the highest risk of metastatic disease, but over half of metastatic PCC/PGL are from sporadic cases without known germline pathogenic variants. Metastatic disease can occur at initial diagnosis or even 20 years after initial diagnosis. Therefore, all patients with PCC/PGL should have lifelong monitoring for recurrence.

16. Why is blood pressure response variable among patients with pheochromocytoma or paraganglioma?

The physiologic response to secretory PCC/PGL can vary depending on the predominantly secreted hormone. Norepinephrine, which can be produced from PCC or PGL, activates both α-1 and β-1 receptors. Hypertension may be more persistent and less episodic. Epinephrine also acts on α-1 and β-1 receptors, but unlike norepinephrine, epinephrine also acts at the α-2 receptor, which can lower sympathetic tone. Epinephrine also uniquely activates the β-2 receptor, which causes skeletal muscle vasodilation and increased norepinephrine release. Thus, epinephrine secretion may cause more paroxysmal hypertension alternating with bouts of orthostatic hypotension.

17. How are pheochromocytomas and paragangliomas diagnosed?

Most PCCs/PGLs are diagnosed incidentally based on imaging findings. For patients with hypertension or other symptoms, the screening test of choice is plasma free metanephrines or 24-hour urine fractionated metanephrines. The silent or intermittently secreting tumors in these patients are continuously metabolizing catecholamines to metanephrines without consistently secreting the parent amines into circulation. Catecholamines should not be measured for initial screening, at least not without metanephrines. Catecholamine levels may be normal or only elevated during a paroxysmal attack in patients with PCC/PGL. Plasma catecholamines are also more prone to false positive elevations due to assay interference. Normal plasma or urinary metanephrines reliably exclude a secreting PCC/PGL. A two- to threefold elevation of plasma free metanephrines above the normal range is associated with nearly 100% probability of a secreting tumor. Per guidelines, plasma free metanephrines should be drawn from an indwelling catheter with the patient supine for 20–30 minutes following an overnight fast. While this may not always be possible in a busy clinical setting, a supine level should at least be considered if there are indeterminate results after blood drawn while sitting up. Often, indeterminate results are due to interfering medications (see upcoming section). When plasma or urine fractionated metanephrines are indeterminate, further testing is warranted.

18. What is the differential diagnosis of hyperadrenergic spells?

Other psychological, neurologic, pharmacological, endocrine, and cardiovascular etiologies of hyperadrenergic spells include panic disorder, hyperventilation, postural orthostatic tachycardia syndrome (POTS), migraine headaches, cocaine or methamphetamine ingestion, withdrawal of adrenergic–inhibitor, sympathomimetic drug ingestion, hypoglycemia, thyrotoxicosis, labile primary hypertension, orthostatic hypotension, paroxysmal cardiac arrhythmia, idiopathic flushing, and diaphoretic spells.

19. What medications can interfere with measurement of plasma or urinary metanephrines?

Now that most plasma metanephrines testing is done with liquid chromatography-mass spectrometry (LC-MS), false-positive results are caused by medications that interfere with the disposition of catecholamines (Table 34.2).

20. What is the clonidine suppression test?

The clonidine suppression test used to be done in cases where plasma metanephrines were only mildly elevated, usually due to increased basal sympathetic activity rather than secondary to a catecholamine-secreting tumor. Clonidine, a centrally acting α-2 adrenoreceptor agonist, would be given to inhibit neuronal norepinephrine release. This would lower metanephrines in patients without PCC/PGL but not in patients with autonomous PCC/PGL–related catecholamine secretion. To do the test, sympatholytic drugs (i.e., β-blockers) are discontinued at least 48 hours before testing. After 20 minutes of supine rest, baseline plasma free metanephrines are drawn from an indwelling venous catheter. Clonidine 0.3 mg is administered, and a second plasma metanephrines level is drawn 3 hours later. The test is considered positive for secretory PCC/PGL if plasma normetanephrine levels at 3 hours do not drop more than 40% when compared with

TABLE 34.2 Medications that Interfere With Measurement of Plasma and Urine Normetanephrine and Metanephrine

	Plasma		*Urine*	
	NORMETANEPHRINE	**METANEPHRINE**	**NORMETANEPHRINE**	**METANEPHRINE**
Acetaminophen	↑↑	–	↑↑	–
Labetalol	–	–	↑↑	↑↑
Sotalol	–	–	↑↑	↑↑
α-Methyldopa	↑↑	–	↑↑	–
Tricyclic antidepressants	↑↑	–	↑↑	–
Buspirone	–	↑↑	–	↑↑
Phenoxybenzamine	↑↑		↑↑	–
MAO-inhibitors	↑↑	↑↑	↑↑	↑↑
Sympathomimetics	↑	↑	↑	↑
Cocaine	↑↑	↑	↑↑	↑
Sulfasalazine	↑↑	–	↑↑	–
Levodopa	↑	↑	↑↑	↑

MAO-inhibitors, Monoamine oxidase inhibitors.
Table adapted from Lenders JWM, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2014;99:1915–1942.

the initial value. Due to improvements in the laboratory assays for plasma and urine metanephrines, this test is rarely required.

21. What is the best diagnostic method to localize a pheochromocytoma or paraganglioma?

Imaging studies should only be ordered when the diagnosis of PCC/PGL has been clearly established. Most tumors are detectable by computed tomography (CT) or magnetic resonance imaging (MRI). CT of the abdomen and pelvis with and without contrast is typically the recommended initial localizing procedure. Adrenal PCC will have precontrast Hounsfield units (HU) greater than 10 in 99.9% of cases. On MRI, PCC will have no loss of signal on in and out of phase imaging, and PCC/PGL will be bright on T2 imaging (lightbulb sign).

22. What other modalities are useful for localization of pheochromocytomas?

PCCs/PGLs express somatostatin receptors, which enable radionuclide imaging with the somatostatin analog DOTATATE labeled with either gallium-68 or copper-64 for PET/CT imaging. DOTATATE PET/CT has high sensitivity and specificity for PCC/PGL, especially in the setting of metastatic disease, with detection rates ranging from 92–100%.

Scintigraphic localization with ^{123}I-metaiodobenzylguanidine (MIBG) is not very sensitive for PCC/PGL, as only 60% are avid. MIBG scans may be useful in the setting of metastatic disease if treatment with ^{131}I MIBG is being planned. MIBG is actively concentrated by sympathomedullary tissue and is subject to interference by drugs that block reuptake of catecholamines, such as tricyclic antidepressants, calcium channel blockers, and labetalol.

^{18}F-FDG PET/CT can be used but is not as sensitive as DOTATATE PET/CT.

23. Which patients with pheochromocytoma or paraganglioma should undergo genetic testing?

All patients presenting with PCC/PGL should be offered clinical genetic testing. Up to 40% of patients with PCC/PGL have germline pathogenic variants in known susceptibility genes. Therefore, confirming a hereditary syndrome in the proband will inform screening and surveillance guidelines for the individual and may result in early detection of PCC/PGL in their relatives.

24. How are pheochromocytomas and paragangliomas treated?

Surgical resection is the only definitive therapy for PCC/PGL. Laparoscopic adrenalectomy is recommended for most PCCs. Open resection is recommended for large or invasive PCCs to ensure complete tumor resection and prevent tumor rupture.

For PGLs, open resection is suggested. Laparoscopic resection can be an option in patients with small and noninvasive PGLs in surgically favorable locations.

For parasympathetic HNPGL, surgical resection, active observation, and radiation are all reasonable treatment possibilities, depending on patient age, tumor size, and tumor location. Multidisciplinary tumor boards should be used to make treatment decisions.

25. Why is preoperative preparation with alpha blockade recommended?

Alpha blockade for sympathetic PCC/PGL, starting 10–14 days before surgery, reduces the incidence of serious and potentially life-threatening catecholamine–induced perioperative complications, including hypertensive crises, cardiac arrhythmias, cardiac ischemia, and pulmonary edema. With adequate pretreatment, perioperative mortality has fallen to less than 1%. While phenoxybenzamine (a longer-acting, noncompetitive α-blocker) has traditionally been recommended as pretreatment of choice, doxazosin (a shorter-acting, competitive α-blocker) is also considered a first-line therapy. Phenoxybenzamine is often difficult to obtain and can be expensive. A randomized prospective trial and several retrospective cohorts have shown no difference in outcomes with either medication. Phenoxybenzamine is started at 10 mg twice daily and typically advanced up to 60 mg/day as needed and tolerated. Doxazosin is started at 2–4 mg per day and usually advanced to around 12–20 mg daily. These medications should be titrated to a goal blood pressure of <110–120/80 mm Hg. Patients might develop orthostasis or mild tachycardia, which may represent adequate α-blockade or hypovolemia. When this happens, patients should be encouraged to liberally consume sodium and fluids. Beta-blockers can be added if tachycardia persists after this with goal heart rates <90 bpm.

26. What is the role of β-blockers and other agents in the preoperative period?

Patients might develop compensatory tachycardia with adequate α-blockade. The use of β-blockers is indicated to control tachycardia and target a heart rate <90 bpm. However, these medications should be initiated only after administration of α-blockers. The initiation of β-blockers in the absence of α-blockade may precipitate a hypertensive crisis due to unopposed stimulation of α-adrenergic receptors. Both β-1–selective and nonselective β-adrenergic receptor blockers can be used. Typical doses of β-blockers include atenolol 25–50 mg per day, metoprolol 12.5–50 mg twice daily, or propranolol 10–40 mg three times per day and can be started at least 3 days after α-blockers have been initiated. Labetalol, which has more potent β than α antagonistic activity, should be avoided as initial therapy. Calcium–channel blockers, such as amlodipine, are the most frequently used addon drug class to further improve blood pressure control in patients already taking α-blockers.

Intraoperative hypertension associated with tumor manipulation may be controlled with either IV phentolamine, nifedipine, or nitroprusside. Postoperative hypotension may be minimized by high fluid intake and a diet rich in sodium.

27. What is the risk of pheochromocytoma/paraganglioma metastases?

Around 10–20% of patients with PCC/PGL will develop metastatic disease, which may occur many years after initial diagnosis. While there are no definitive risk factors for metastasis, tumor size (>5 cm for PCC and >4 cm for PGL), gross large vessel invasion, *SDHB* germline pathogenic variants, persistently elevated postop catecholamine levels, and young age at initial diagnosis may increase metastatic risk. On pathologic examination, higher Ki-67 or mitotic index may also increase risk. Because all PCC/PGL have the potential to metastasize, all patients require long-term follow-up and surveillance.

28. How are metastatic pheochromocytomas and paragangliomas treated?

There are no curative treatments for metastatic PCC/PGL. Surgical resection or debulking can help, especially in cases of secreting disease. For patients with unresectable disease, other treatment modalities are available, including external beam radiation therapy for painful bone metastases, percutaneous radiofrequency ablation or transarterial chemoembolization for liver metastases, and cryoablation or percutaneous ethanol injection for metastatic lesions at a variety of sites. Radionuclide therapy, chemotherapy, and targeted agents can be used as well. Referral for clinical trials is also an option.

29. Discuss the role of radionuclide therapy and chemotherapy.

Treatment with ^{131}I-MIBG should be considered in patients with a positive ^{123}I-MIBG scan when there are unresectable progressive tumors not amenable to locoregional methods of control. Conventional MIBG therapy has been used for years. High-specific activity MIBG was FDA approved for metastatic PCC/PGL but is no longer being offered due to financial constraints. Off-label treatment with peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE should be considered in patients with DOTATATE avid disease. Clinical trials are ongoing in this population, as the therapy is already approved for gastroenteropancreatic neuroendocrine tumors. Other therapies for which partial tumor responses have been reported in patients with progressive disease include chemotherapy with cyclophosphamide, vincristine and dacarbazine or temozolomide. Encouraging partial responses in subgroups of patients have also been reported with the tyrosine kinase inhibitors sunitinib and cabozantinib. Clinical trials with other targeted agents, including HIF inhibitors, are underway.

30. What is the prognosis for metastatic pheochromocytomas and paragangliomas?

The clinical course of patients with metastatic PCC/PGL is highly variable, with some patients living more than 20 years after diagnosis. The overall 5-year survival rate is approximately 50–69%. Rapid disease progression is associated with male sex, older age, large primary tumor size, synchronous metastases, elevated dopamine levels, and an unresected primary tumor.

31. What is the molecular taxonomy of catecholamine–secreting tumors?

PCC/PGL seems to fall into three categories based on transcriptomic analysis of the tumor tissue.

1. Pseudohypoxic PCC/PGL: upregulation of hypoxia signaling pathways is seen on transcriptome analysis of some PCC/PGL. Under pseudohypoxia (a situation where oxygen is present but cannot be processed because of an alteration in oxygen-sensing pathways), hypoxia-inducible factors (HIFs) are produced in large amounts leading to transcription of hypoxia-responsive genes, which are involved in tumorigenesis.
    - TCA cycle–related: a majority of patients with tumors in this category have familial PGLs associated with germline pathogenic variants in *SDHx* (x = A, B, C, D, or AF2) genes. Mutations of these genes prevent the oxidation of succinate to fumarate, thus impeding the respiratory electron transfer chain. A minority of patients can have pathogenic variants in other TCA cycle genes, including *Fumarate Hydratase (FH)*, which then prevents the conversion from fumarate to malate. These genes rarely have somatic mutations found in PCC/PGL.
    - *VHL/EPAS1*–related: patients with germline pathogenic variants in *VHL* have von Hippel-Lindau syndrome. Some patients have germline or mosaic gain-of-function mutations in *EPAS1* leading to PCC/PGL, polycythemia, and somatostatinomas. Alternations in both genes also induce a pseudohypoxia state. Both *VHL* and *EPAS1* also can be somatically mutated in PCC/PGL.
    - Sporadic-related tumors: some tumors with no known germline pathogenic variants or known somatic variants will also fall in this category.
2. Kinase signaling PCC/PGL: activation of kinase signaling pathways are seen on transcriptome analysis of some PCC/PGL tumor tissue.
    - Germline pathogenic variants: tumors in this group have germline pathogenic variants in susceptibility genes involved in kinase signaling. The most common alterations are gain-of-function variants in *RET*, leading to MEN2. Some patients have germline pathogenic variants in *NF1* (leading to Neurofibromatosis type 1) and *TMEM127* and *MAX* (both leading to familial paraganglioma syndromes). These cases are due to activation of kinase signaling pathways that induce tumorigenesis, including the RAS, MAPK and PI3K pathways.
    - Somatic mutations: some PCC/PGL do not have known germline pathogenic variants in susceptibility genes but have tumor specific, somatic variants, in these same genes or others in the kinase signaling pathways. Some common somatic mutations are found in *HRAS*, *NF1*, and *RET*.
    - Sporadic-related tumors: some tumors with no known germline pathogenic variants or known somatic variants will also fall in this category.
3. WNT signaling PCC/PGL: PCC/PGL in this class are defined by altered WNT signaling seen on transcriptome analysis. Typically, these tumors are from patients with sporadic PCC/PGL (meaning no identified germline pathogenic variant) and the tumors often have somatic mutations in *CSDE1,* or have somatic fusion genes involving upregulation of *MAML3*.

KEY POINTS

PCC and PGL

- PCC and PGL are neuroendocrine tumors of the autonomic nervous system that may or may not secrete catecholamines.
- Secretory PCCs/PGLs may present with hypertension, diaphoresis, palpitations, or headaches, but many do not produce classic symptoms.
- Eighty percent of catecholamine-secreting tumors are PCCs and 20% are PGLs.
- The best screening tests for secretory PCC/PGL are plasma free metanephrines or 24 hour urine metanephrines.
- The most cost-effective tumor localization is accomplished with computed tomography or magnetic resonance imaging. Nuclear medicine imaging (DOTATATE-PET) is more sensitive, specific, and useful, especially for determining the extent of metastatic disease.
- Therapy for primary PCC/PGL is typically surgical resection after administration of alpha blockade. For head and neck PGL, active observation, resection, or radiation are used depending on the tumor location and patient age and preference.
- About 30–40% of patients with PCC/PGL have a germline pathogenic variant in one of over 12 well-defined susceptibility genes.
- Every patient with PCC/PGL should be offered clinical genetic testing and consultation with a genetic counselor.

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Adrenal Incidentalomas

Michael T. McDermott

1. What is the definition of an adrenal incidentaloma?

Adrenal incidentalomas are adrenal masses >1 cm in largest dimension that are discovered incidentally during abdominal imaging procedures that are ordered for unrelated reasons. Adrenal incidentalomas may be unilateral or bilateral.

2. How common are incidentally discovered adrenal masses?

Adrenal incidentalomas are estimated to be present in 7–10% of all people undergoing abdominal imaging. They are more common in older individuals (estimated prevalence approximately 10% in the older population and approximately 1% in people <30 years old). Unilateral adrenal masses account for 85–90% of incidentalomas while 10–15% are bilateral.

3. What are the most common etiologies of a unilateral adrenal incidentaloma?

Nonsecreting Adenomas	85%
Cortisol Secreting Adenomas	6.4%
Pheochromocytomas	3.1%
Adrenocortical Carcinomas	1.9%
Aldosterone Secreting Adenomas	0.6%

4. What are the most common causes of bilateral adrenal incidentalomas?

Bilateral adrenal incidentalomas are most often a result of metastatic cancer, congenital adrenal hyperplasia, nonfunctioning adrenal adenomas, primary aldosteronism (bilateral adrenal hyperplasia and other bilateral conditions), pheochromocytoma (especially familial), ACTH-dependent Cushing's syndrome (ACTH-secreting pituitary adenomas, ectopic ACTH-secreting tumors), bilateral macronodular adrenal hyperplasia (BMAH), adrenal hemorrhage (most often in the setting of trauma, coagulopathy, systemic anticoagulation), tuberculosis, deep fungal infections, lymphomas, and infiltrative diseases (amyloidosis, hemochromatosis).

5. What are the goals of the evaluation of adrenal incidentalomas?

The evaluation of unilateral adrenal incidentalomas must determine if the adrenal mass is benign or malignant and if the mass is secreting adrenal hormones. Approximately 2% of adrenal incidentalomas are malignant and about 10% secrete excess hormones. For bilateral adrenal masses, the goals are the same in addition to evaluating for the disorders, listed above, that cause enlargement or masses in both adrenal glands.

6. Identify clinical features that are helpful in the evaluation of adrenal incidentalomas.

Symptoms and signs of cortisol excess (moon facies, facial plethora, dorsocervical fat pad, central obesity, violaceous striae, easy bruising, proximal muscle weakness, hyperglycemia, hypertension, osteoporosis), aldosterone excess (hypertension ± hypokalemia), catecholamine excess (hypertension, headaches, palpitations, sweating), and androgen excess (hirsutism, acne) are critical clues that point to overt adrenal cortical or medullary hormone hypersecretion.

7. Why is the lipid content of an adrenal incidentaloma important?

The lipid content of an adrenal incidentaloma is a key feature. Lipid-rich adrenal masses arise in the adrenal cortex and are almost universally benign; they are either nonsecretory or autonomously secrete cortisol or aldosterone. Lipid-poor adrenal masses can be benign secretory or nonsecretory adenomas but can also be pheochromocytomas, adrenocortical carcinomas, or metastatic carcinomas.

TABLE 35.1 CT Adrenal Mass Protocol

	NCCT	CECT	DCECT	RWP
Adenoma	<10 HU	Enhance	<30 HU	>50%
Pheochromocytoma	>10 HU		>30 HU	<50%
Carcinoma	>20 HU		>30 HU	<50%
Metastatic Cancer	>20 HU		>30 HU	<50%

TABLE 35.2 MRI Adrenal Mass Imaging (compared to liver: T1/T2 weighted images)

Adenoma	Intensity Versus Liver: Isodense (T1 and T2); Signal Dropout
Pheochromocytoma	Intensity Versus liver: high (T2)
Carcinoma	Intensity Versus liver: lower (T1); high/intermediate (T2)
Metastatic Cancer	Intensity Versus liver: isodense or low (T1); high/intermediate (T2)

8. How do you determine the lipid content of an adrenal mass?

Lipid content is best determined by CT or MR imaging. On noncontrast CT (NCCT), Hounsfield Units (HU) < 10 indicate a lipid-rich mass and HU >20 indicate a lipid-poor mass. HU values of 10–20 are indeterminate. On MR, isodensity with the liver and signal dropout on out-of-phase sequencing indicates a lipid-rich mass. More extensive CT protocols can include an NCCT, contrast-enhanced CT (CECT), delayed contrast–enhanced CT (DCECT), and relative washout percentage (RWP). Tables 35.1 and 35.2 show how these studies are interpreted.

9. What other imaging features are useful in the evaluation of adrenal incidentalomas?

Besides high lipid content (HU <10), benign adrenal adenomas tend to be small (<4 cm), round, and homogeneous and have smooth borders. In addition to low lipid content (HU >20), adrenocortical carcinomas are usually large (>4 cm) and heterogeneous and have calcifications, irregular borders, local invasion, and lymphadenopathy. These features are also important to evaluate with masses that have indeterminant HU values of 10–20.

10. What are the best tests to evaluate for excess cortisol secretion by an adrenal incidentaloma?

If overt signs and symptoms of hypercortisolism are present, a 24-hour urine cortisol, bedtime salivary cortisol, or a 1-mg overnight dexamethasone suppression test (DST) will all likely be abnormal. To detect mild autonomous cortisol secretion (MACS), a 1-mg DST is the best test. For the DST, dexamethasone 1 mg is given at bedtime and serum cortisol and dexamethasone levels are drawn at 8:00 a.m. the next morning. Interpretation of the 1-mg DST is as follows:

AM Cortisol Interpretation

<1.8 µg/dl	Normal
1.8–5.0 µg/dl	Borderline
>5.0 µg/dl	Autonomous cortisol secretion

A dexamethasone level >200 ng/dl (4.5 nmol/L) is necessary for the test to be accurate.

11. Why is the measurement of DHEAS useful?

Dehydroepiandrosterone sulfate (DHEAS) is secreted by the adrenals under the regulation of ACTH; the half-life of DHEAS is 10–16 hours. DHEAS therefore represents a durable indicator of endogenous ACTH secretion. Excess cortisol production from an adrenal adenoma suppresses ACTH secretion, resulting in a low serum DHEAS level. A 2017 study demonstrated that a DHEAS ratio ≤1.12 (DHEAS ratio: divide DHEAS level by the lower limit of the DHEAS reference range) has 99% sensitivity and 92% specificity for autonomous cortisol secretion. This test, therefore, appears to be useful and complementary to the DST.

12. What can cause a false-positive overnight dexamethasone suppression test?

Oral estrogens significantly increase hepatic production of cortisol-binding globulin (CBG) to which circulating cortisol is bound. Serum total cortisol levels increase by approximately 67% in women who take oral contraceptive pills (OCP), causing false-positive elevations of baseline and post-DST cortisol levels. Pregnancy has the same effect. It is best, when possible, to perform the DST after stopping OCP for 2 months or screen with a test that measures free cortisol (24-hour urine cortisol, bedtime salivary cortisol), although these are less sensitive for detecting MACS.

13. Is mild autonomous cortisol secretion (MACS) associated with comorbidities?

MACS (also called subclinical Cushing's syndrome) has been reported to be associated with a higher prevalence of type 2 diabetes mellitus, hypertension, osteoporosis, cardiovascular disease, and overall mortality. Prevention or resolution of these comorbidities by treatment of MACS, however, has not been well studied.

14. When and how should a patient with an adrenal incidentaloma be assessed for primary aldosteronism?

Testing for primary aldosteronism in the setting of an adrenal incidentaloma is recommended only for those people who also have hypertension. Plasma aldosterone (PA) and plasma renin activity (PRA) should be measured. Screening is considered positive when PA >5 ng/dl, PRA is <1 ng/ml/hour, and the aldosterone to renin ratio (ARR) is >20. Confirmatory testing for primary aldosteronism and possible adrenal vein sampling would then be considered as discussed in the chapter on primary aldosteronism.

15. What tests are recommended to determine if an adrenal incidentaloma is a pheochromocytoma?

Pheochromocytomas are lipid poor (HU > 10 but usually >20) and often have a characteristic imaging phenotype on CT and MR (see above). If imaging features are suggestive of a pheochromocytoma (high pretest probability), a high-sensitivity test is best; plasma metanephrines (sensitivity 95–98%; specificity 89–95%) is best. If imaging is not strongly suggestive of a pheochromocytoma (low to moderate pretest probability), a test with higher specificity (24-hour urinary metanephrines and catecholamines) is best.

16. Develop an algorithm for the hormone evaluation of a unilateral adrenal incidentaloma.

See Fig. 35.1.

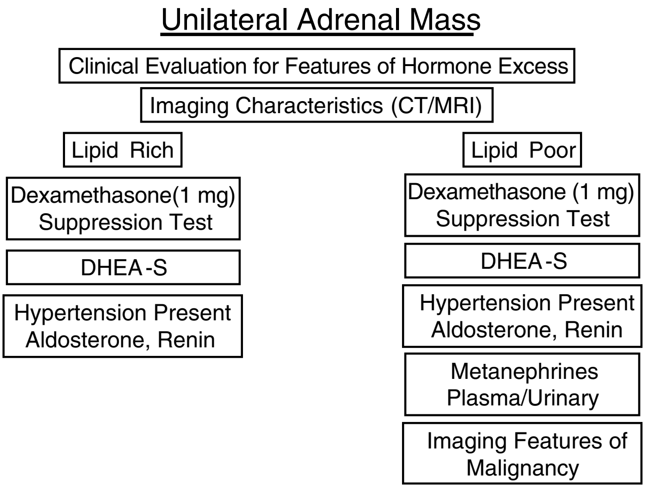
Unilateral Adrenal Mass
Clinical Evaluation for Features of Hormone Excess
Imaging Characteristics (CT/MRI)
Lipid Rich
Dexamethasone(1 mg) Suppression Test
DHEA-S
Hypertension Present Aldosterone, Renin
Lipid Poor
Dexamethasone (1 mg) Suppression Test
DHEA-S
Hypertension Present Aldosterone, Renin
Metanephrines Plasma/Urinary
Imaging Features of Malignancy

Fig. 35.1 Evaluation of a Unilateral Adrenal Incidentaloma. Lipid-rich (HU <10 on CT or liver isodensity and signal dropout on MR). Lipid-poor (HU >20 on CT or lack of liver isodensity and no signal dropout on MR).

TABLE 35.3 Recommended Initial Management of Adrenal Incidentalomas

Surgery Recommended
Pheochromocytoma
Cushing's syndrome
Primary aldosteronism
Adrenocortical carcinoma
Mass size >4 cm
Growth (>1 cm per AACE guidelines; >5 mm or >20% per European guidelines)
Consider for all lipid-poor masses

Surgery or Close Monitoring Based on Clinical Judgment
Mild autonomous cortisol secretion (MACS) without clinical Cushings' features

Surgery and Monitoring Not Necessary
Nonsecreting lipid-rich adenoma
Myelolipoma (HU <0)

17. What additional evaluation should be done when there are bilateral adrenal masses?

The evaluation for bilateral adrenal masses is similar to that for unilateral adrenal masses, but additional testing should include a plasma ACTH (to rule out ACTH-dependent Cushing's syndrome), serum 17 OH progesterone (to rule out CAH), and, depending on the history and physical exam, consideration and additional testing for adrenal hemorrhage (trauma, coagulopathy, systemic anticoagulation), tuberculosis, deep fungal infections, lymphomas, and infiltrative diseases (amyloidosis, hemochromatosis) may be warranted.

18. When should an adrenal mass be biopsied?

Biopsy of an adrenal mass should be strictly avoided if suspicion for adrenocortical carcinoma or pheochromocytoma is moderate to high. Biopsy of an adrenocortical carcinoma poses a significant risk of malignant cell spillage from the tumor. Biopsy of pheochromocytoma can precipitate a hypertensive crisis due to the sudden release of large amounts of catecholamines from the tumor. A biopsy should be considered when an adrenal mass is discovered in a patient who has another primary malignancy to determine if the adrenal mass is metastatic cancer.

19. How should the incidentally discovered adrenal mass be managed?

See Table 35.3.

20. Which adrenal incidentalomas can show positive uptake on positron emission tomography (PET, PET/CT) scanning?

PET positivity has been reported in both malignant and benign adrenal masses. Positive uptake is most common in adrenocortical carcinomas, metastatic cancers, pheochromocytomas, adrenal tuberculosis, and adrenal lymphoma but may also occur with bilateral adrenal hyperplasia due to ACTH-dependent Cushing's syndrome (ACTH-secreting pituitary tumors and ectopic ACTH-secreting tumors), ganglioneuromas, adrenal adenomas (approximately 3%), and myelolipomas (rarely). CT/PET scanning has not yet been well studied in adrenal incidentalomas.

21. When surgery is not indicated, how should an adrenal incidentaloma be monitored?

Repeat CT or MR is recommended 3–6 months after the initial evaluation and at 1 and 2 years. If there is no growth, further imaging may not be necessary, but clinical judgment must be used. If the mass enlarges by >1 cm (AACE guidelines) or >5 mm or 20% (European guidelines), surgery is recommended because it may be an adrenocortical carcinoma that was diagnosed at an early stage. It is recommended that the overnight 1-mg DST be repeated yearly for 5 years, because MACS can be subtle and often increases over time. If other hormone testing was normal on the initial evaluation, repeat testing for hormone excess, other than cortisol, is not necessary.

KEY POINTS

- Incidentally discovered adrenal masses are most often benign nonfunctioning adrenal cortical adenomas.
- The goal of an adrenal incidentaloma evaluation is to determine if the mass is malignant or is secreting excess adrenal hormones.
- The different types of adrenal masses often have characteristic phenotypes on cross-sectional imaging that make or strongly suggest a specific diagnosis. Lipid-rich masses (Hounsfield units <10 on noncontrast CT) are benign. Lipid-poor masses (Hounsfield units >20 on noncontrast CT) may be malignant or benign.
- The most common hormonal abnormality seen with adrenal incidentalomas is mild autonomous cortisol secretion, which is associated with comorbidities.
- Adrenal biopsies should not be done if there is any suspicion that the adrenal mass is an adrenocortical carcinoma or pheochromocytoma.
- Surgery is indicated for adrenal incidentalomas when they are diagnostic of or suspicious for adrenocortical carcinoma or pheochromocytoma, if they secrete excess adrenal hormones, if they are >4 cm in size, or if they grow >5 mm or 20% on follow-up imaging studies.

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CHAPTER 36

Adrenal Malignancies

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1. What types of cancer occur in the adrenal glands?

Adrenocortical carcinomas (ACC) arise in the adrenal cortex and pheochromocytomas develop in the adrenal medulla. ACC is a rare cancer, affecting approximately 0.7–2 adults per million population per year. Metastatic pheochromocytomas are similarly rare at 2–8 per million. The World Health Organization (WHO) no longer characterizes pheochromocytoma as benign or malignant, but rather localized or metastatic. All pheochromocytomas in the adrenal gland have the potential to metastasize. In addition, metastatic cancer from primary malignancies in other organs (small-cell carcinoma of the lung, renal cell carcinoma, melanoma, gastric adenocarcinoma, hepatocellular adenocarcinoma, esophageal adenocarcinoma, and breast carcinoma) may also be seen in the adrenal glands.

2. How do adrenocortical carcinomas present clinically?

ACC may present with symptoms and signs of excess steroid hormone secretion (<40–60%), with tumor mass effects of abdominal or flank pain (<33%), or as an incidentally discovered adrenal mass found during abdominal imaging ordered for unrelated reasons (<20–30%).

3. What clinical features are seen with steroid hormone–secreting adrenocortical carcinomas?

Functioning ACC secrete cortisol, androgens, aldosterone, or estrogens—alone or sometimes in combination. Cortisol overproduction is most common (40–60% of cases) and results in Cushing's syndrome. Androgen secretion, seen in <25% of cases, causes hirsutism and virilization in women, and precocious puberty in children. Aldosterone secretion causes hypertension and hypokalemia (Conn's syndrome/primary aldosteronism). Estrogen production (rare) causes menstrual disturbances in women, and gynecomastia and hypogonadism in men. If a patient with an adrenal mass presents with combined hormone secretion, there is a high suspicion of an ACC rather than a benign adrenal adenoma.

4. What imaging features are most suggestive of an adrenocortical carcinoma?

A noncontrast–enhanced abdominal computed tomography (NCCT) is the best overall imaging test to assess an adrenal mass (Table 36.1). Features that most strongly suggest ACC are size >4 cm, heterogeneity, calcifications, irregular borders, local invasion, lymphadenopathy, and decreased lipid content. Lipid content is assessed by signal attenuation, expressed in Hounsfield units (HU); low HU is indicative of high lipid content, and high HU is indicative of low lipid content. ACC typically has very low lipid content, yielding HU >20 on NCCT. An adrenal mass CT protocol is employed in many institutions utilizing NCCT, followed by contrast-enhanced CT (CECT), delayed contrast-enhanced CT (DCECT; 10–15 minutes postcontrast injection), and calculation of relative washout percentage (RWP). ACC typically shows HU >20 on NCCT, HU >30 on DCECT, and <40% RWP. Magnetic resonance imaging (MRI) can also be used to assess the size and features of adrenal masses. Assessment of chemical shift (homogenous signal dropout on in-phase compared to opposed-phase imaging) on MRI can be helpful in assessing lipid content. Compared to malignant masses, benign adrenal adenomas have preserved chemical shifts. MRI does not distinguish ACC from pheochromocytomas or metastatic masses. Fluorodeoxyglucose positron emission tomography (FDG-PET) or PET/CT fusion scanning may also be useful, especially for identifying metastatic or recurrent diseases.

5. What biochemical evaluation should be undertaken in patients with an adrenal mass suspected of adrenocortical carcinoma?

Biochemical evaluation should include morning cortisol, ACTH, DHEA-S, total testosterone, estradiol, aldosterone, and renin. Additional evaluation for hypercortisolism, including

TABLE 36.1 Imaging Features of Benign Versus Malignant Adrenal Mass

	BENIGN	MALIGNANT
Size	<4 cm	>4 cm
Margins	Smooth, rounded	Irregular
Calcifications	None	Common
Necrosis	Rare	Common
Noncontrast CT Scan Features		
Hounsfield Units	<10	>20
Relative contrast washout (10–15 min)	High (>40%)	Low (<40%)
MRI features		
Chemical Shift (homogenous signal drop on opposed-phase imaging)	Yes	No
FDG-PET	Low uptake	High uptake

1-mg dexamethasone suppression test and/or 24-hour urinary-free cortisol excretion, should be performed. Profiling of additional steroid precursors in plasma including 11-deoxycortisol, androstenedione, 17-beta-estradiol, and 17-hydroxyprogesterone, can also be considered. A recent study found that metabolites of 11-deoxycortisol and DHEA-S might be the most useful discriminative markers between benign and malignant adrenal tumors, although this has yet to be confirmed in larger cohorts. These hormones may be elevated even in the setting of nonfunctional ACC tumors. In addition, a 24-hour urine steroid metabolic panel was recently introduced as a novel clinical tool for detecting malignancy in adrenal tumors. Plasma metanephrines should be checked to rule out pheochromocytoma. Blood glucose/HbA1c should also be considered to evaluate for comorbid metabolic issues.

6. Should a biopsy of adrenal masses suspicious of adrenocortical carcinoma be performed?

Biopsy of potentially resectable masses for which there is moderate-to-high suspicion of ACC should not be performed because of the risk of spillage of malignant cells from the tumor. A biopsy should be considered when an adrenal mass is present in a patient who has another primary malignancy with known metastases to determine whether the adrenal mass is metastatic cancer from the other tumor. If a biopsy is to be performed, it is imperative to rule out pheochromocytoma first with plasma-free metanephrines or 24-hour urine fractionated metanephrines.

7. What histologic features are characteristic of an adrenocortical carcinoma?

The modified Weiss Scoring System is most commonly used. This system evaluates five characteristics and assigns a score: >5 mitoses/50 high power fields (score from 0–2), clear cells comprising <25% of the tumor (0–2), atypical mitoses (0–1), necrosis (0–1) and capsular invasion (0–1). ACC is diagnosed with a score ≥3 and is further classified as low grade (<20 mitoses per 50 high-power fields or Ki67 expression <10%) and high grade (>20 mitoses per 50 high-power fields or Ki67 expression >10%).

8. What inherited or acquired genetic abnormalities might cause adrenocortical carcinoma?

In adults, approximately 3–7% of ACC are associated with germline *TP53* pathogenic variants and 3% are associated with germline pathogenic variants in mismatch repair genes (Lynch's syndrome). ACC in children often occurs in the setting of germline *TP53* pathogenic variants (Li Fraumeni's syndrome) or *IGF-2* locus imprinting defects (Beckwith-Weidemann syndrome) (Table 36.3). A recent comprehensive genome analysis by the Cancer Genome Atlas (TCGA) confirmed that about 60% of ACC have somatic (tumor-specific) driver mutations either in the *TP53*/tumor suppressor pathway (20%) or the B-catenin/Wnt pathway (40%). The remaining 40% of tumors have uncommon or unknown drivers. Clinically modulating IGF-2 in ACC

TABLE 36.2 5-Year Disease-Free Survival for Adrenocortical Carcinoma According to European Network for the Study of Adrenal Tumors (ENSAT) 2008 Staging System

STAGE	AJCC/ENSAT TNM STAGING			5-YEAR SURVIVAL
I	T1	N0	M0	82%
II	T2	N0	M0	61%
III	T1-2 T3-4	N1 N0-1	M0 M0	50%
IV	T1-4	N0-1	M1	13%

was investigated after *in vitro* targeting yielded promising antitumor activity; however, this did not translate into success in clinical trials. Antiangiogenics or epidermal growth factor receptor (EGFR)–targeted drugs in patients with ACC also have yielded disappointing results. Frequent amplifications of the *CDK4, FGFR1, FGF9, and FRS2* loci and frequent deletions in *CDKN2A* and *CDKN2B* suggest molecular abnormalities in genes governing cell cycle transitions; however, none of the currently known somatic mutations have been successfully translated into a therapeutic strategy.

9. Describe the most commonly used staging systems for adrenocortical carcinoma.

ACCs are first classified by their Tumor Node Metastasis (TNM) status. T refers to the primary tumor: TX – cannot be assessed; T0 – no evidence of primary tumor; T1 – tumor <5 cm, no extraadrenal disease; T2–tumor >5 cm, no extraadrenal disease; T3 – tumor any size, local invasion but not into local organs; T4 – tumor any size, invades local organs or large vessels. N refers to regional lymph nodes: NX – cannot be assessed; N0 – nodes absent; N1 – nodes present. M refers to distant metastases: M0 – metastases absent; M1 – metastases present. The American Joint Committee on Cancer (AJCC) stages tumors as follows: stage 1: T1N0M0; stage 2: T2N0M0; stage 3: T1N1M0, T2N1M0, T3AnyNM0, T4AnyNM0; stage 4: M1. The European Network for the Study of Adrenal Tumors (ENSAT) uses a slightly different staging system: stage 1: T1N0M0; stage 2: T2N0M0; stage 3: T3/T4N0M0, T1/T2/T3/T4N1M0; stage 4: M1 (Table 36.2).

10. What is the distribution of adrenocortical carcinoma stages at diagnosis?

Stage 1: 14%; Stage 2: 45%; Stage 3: 27%; Stage 4: 24%

In early-stage disease (stages 1 and 2), disease-specific 5-year survival ranges from 60% to 80%. In stage 3 disease, 5-year survival decreases to 40–60% (Table 36.2).

11. Describe the preferred initial treatment for adrenocortical carcinoma.

Surgical resection is the only potentially curative strategy and is, therefore, the initial treatment of choice for all resectable stage I–III disease. In patients with advanced disease, surgery is also considered in a setting of overt Cushing's syndrome where resection of the primary tumor might help reduce hypercortisolism. Surgery is also considered in the setting of oligo-metastatic disease where lower volume metastases might be targetable with additional therapies postprimary tumor resection. Recent evidence suggests that surgical expertise correlates with survival in patients with ACC, suggesting that surgery is best done by surgical endocrine/oncology teams at centers where there is significant experience with this condition. Open adrenalectomy is recommended over laparoscopic adrenalectomy by most experts. Removal of suspicious lymph nodes encountered during surgery is recommended. Even in patients with stage I–III disease, recurrence is common, probably because of the presence of undetected micrometastases.

12. When and what type of adjuvant therapy is recommended after resection of an adrenocortical carcinoma?

Because of the high recurrence rate (60–80%), adjuvant therapy with mitotane is recommended for all patients who have ACC with incomplete resections, tumor fracture or spillage during the resection, low-grade large tumors with capsular invasion, or high-grade pathology (>20 mitoses per 50 high-power fields or Ki67 expression >10%). In patients who have evidence of persistent or recurrent disease, combination adjuvant therapy using mitotane plus cisplatin-based chemotherapy, such as etoposide, doxorubicin, and cisplatin (EDP-M), is utilized. Adjuvant tumor bed radiation therapy may also be considered for patients who have incompletely resected tumors, tumor fracture or spillage during surgery, or high-grade pathology.

13. What is mitotane and how is it used?

Mitotane is an adrenally toxic insecticide derivative with significant antitumor efficacy against ACC. The starting dose is 500 mg twice daily with dose escalation to 4–6 g daily (usually divided BID after meals) over the ensuing 4 to 8 weeks. Mitotane metabolism shows significant interindividual variability; therefore, serum mitotane level monitoring every 2–4 weeks is strongly recommended with a goal of maintaining serum mitotane in the 14–20 mcg/mL range. Nausea and GI upset, which can be limiting factors in achieving a therapeutic dose, can usually be managed by premedicating using a proton pump inhibitor and antiemetic (such as ondansetron) before meals. Mitotane has rarely been associated with fulminant liver failure, so monitoring liver enzymes after initiation of therapy is recommended.

14. What effect does mitotane have on adrenal function and how is this managed?

Mitotane causes atrophy and destruction of the adrenal cortex. As a result, it causes adrenocortical insufficiency in virtually all ACC patients except those with very overtly cortisol-producing tumors. Glucocorticoid replacement therapy should, therefore, be started at the same time mitotane therapy is initiated or shortly after. Mitotane potently induces cytochrome P450 enzymes that metabolize cortisol, hydrocortisone, dexamethasone, and fludrocortisone. Therefore, higher glucocorticoid replacement doses are needed in mitotane-treated patients than in those with adrenal insufficiency from other causes. Prednisone 5–7.5 mg twice daily or hydrocortisone 40–60 mg divided into two or three times daily dosing schedules are typically required. Mitotane also raises cortisol–binding globulin (CBG) levels, rendering serum cortisol values inaccurate. Monitoring the adequacy of glucocorticoid dosing is best done by regular clinical assessment for adrenal insufficiency signs and symptoms. Mineralocorticoid replacement is often not needed initially, but regular monitoring of blood pressure, serum potassium and sodium, and plasma renin levels is recommended, with the addition of fludrocortisone therapy if the patient develops hypotension, hyperkalemia, hyponatremia, or elevated plasma renin.

15. What other endocrine effects does mitotane have?

Mitotane suppresses pituitary thyroid–stimulating hormone (TSH) secretion, resulting in central hypothyroidism (low TSH and low free thyroxine [T4]); it also increases serum thyroxine-binding globulin (TBG) levels, which can further lower serum free T4 levels. Levothyroxine replacement should be given to patients who develop central hypothyroidism, and free T4 (not TSH) should be monitored to adjust the dose of levothyroxine. Mitotane also causes hypogonadism in men, often severe enough to require testosterone replacement; and because it also increases sex hormone–binding globulin (SHBG) levels, measurement of total testosterone may underestimate the severity of the testosterone deficiency. In women, the use of mitotane is associated with elevations of both luteinizing hormone and follicle-stimulating hormone, and the development of large ovarian cysts has been reported. Mitotane can also cause substantial hypercholesterolemia.

16. How does the management of cortisol–producing adrenal cancers differ from nonfunctional adrenocortical carcinomas?

Cortisol excess predisposes patients to infections, sepsis, thromboembolic events, poor wound healing, hyperglycemia, and other glucocorticoid effects. Mitotane alone is not usually sufficient to control hypercortisolism. Metyrapone, a steroidogenic enzyme inhibitor, is the most effective agent for reducing cortisol production; the starting dose is 250 mg every 6 hours, with subsequent dose escalation up to a total daily dose of 6 g in divided doses. When metyrapone does not lower cortisol levels sufficiently, ketoconazole, also an enzyme inhibitor, can be added with a starting dose of 200 mg every 8 hours with titration up to a target dose of 400 mg every eight hours. Osilodrostat is a recently FDA-approved cortisol synthesis inhibitor which is effective in the treatment of hypercortisolism with the added convenience of twice daily dosing. If hypercortisolism persists despite the use of the cortisol synthesis inhibitors, the glucocorticoid receptor antagonist mifepristone can also be added. This medication will not lower serum cortisol levels but will block glucocorticoid action at the tissue receptor level and is best used by an experienced endocrinologist as it may be associated with the development of hypertension and hypokalemia. Etomidate, an 11-hydroxylase inhibitor that is administered intravenously, can be given, starting with a dose of 0.3 mg/kg/hr in patients who cannot take oral medications or when serum cortisol levels must be lowered acutely. If primary and adjuvant therapy are effective in reducing the tumor burden, adrenal insufficiency may eventually develop, resulting in a requirement for glucocorticoid and mineralocorticoid replacement therapy, as discussed above.

17. What type and frequency of monitoring is recommended after treatment for adrenocortical carcinomas?

Follow-up imaging with contrast-enhanced CT (CECT) or MRI of the chest, abdomen, and pelvis is recommended every 3 months for 2–3 years and then every 4–6 months for 5 years. FDG-PET/CT imaging at 6-month intervals is recommended by some, but high-quality evidence supporting its routine use is lacking. Regular monitoring of specific steroid hormone production for the hormone–secreting tumors is advocated by some, but others suggest testing these only if clinical signs of hormone excess recur. Patients on mitotane should also have regular assessments every 4–6 weeks of serum mitotane levels (target: 14–20 mcg/mL). Other labs usually followed include a comprehensive metabolic panel (CMP), complete blood count (CBC), thyroid function tests, gonadal steroids in symptomatic patients, and lipid panel.

18. How should unresectable, recurrent, and metastatic adrenal cortical carcinomas be managed?

Primary therapy with mitotane, usually in combination with EDP chemotherapy, is recommended for patients with unresectable or locally recurrent ACC. Radiofrequency ablative therapy may offer additional benefits in select cases. Targeted therapies utilizing tyrosine or multikinase inhibitors, such as cabozantinib, have been shown to have limited efficacy; in the future, the use of these agents might be guided by individual tumor-targeted next-generation sequencing. Immunotherapy using checkpoint inhibitors has also shown some effectiveness, especially in patients with hereditary mismatch repair gene pathogenic variants (Lynch syndrome). Referral to centers doing clinical trials of investigative agents should, therefore, also be considered.

19. What is the prognosis for patients with adrenocortical carcinoma?

The mean survival is 15 months. The 5-year survival rate is <35%. Prognosis is improved with young age, small tumor size, localized disease, complete tumor resection, and nonfunctioning tumors. The two most significant prognostic factors are disease stage and completeness of the initial surgical resection. Grading (low versus high grade as described above) based on mitoses per 50 high-power fields and Ki67 expression adds additional prognostic information. Oncogene and tumor marker assessment is currently being evaluated, but sufficient data to ascribe specific prognostic predictability for the use of molecular markers in a clinical setting is not available. The 5-year disease-free survival rates by disease stage are shown in Table 36.2.

20. How often do pheochromocytomas become metastatic?

Approximately 15–25% of all pheochromocytomas and paragangliomas become metastatic. Unfortunately, there is no good way to predict which pheochromocytomas or paragangliomas will become metastatic. Therefore, all patients who have a pheochromocytoma or paraganglioma should be followed for life.

21. What are the clinical features of metastatic pheochromocytomas?

Pheochromocytomas, localized or metastatic, typically secrete catecholamines and, therefore, cause hypertension, headaches, sweating, and palpitations, but some are asymptomatic. Paragangliomas can arise from either parasympathetic or sympathetic ganglia. Parasympathetic paragangliomas are nonsecretory and, therefore, are often asymptomatic except for mass effects or bone lesions. Pheochromocytomas and sympathetic paragangliomas are diagnosed by finding increased plasma or urinary levels of metanephrines or catecholamines. Plasma and urinary metanephrines have the highest sensitivities and specificities of all available tests. Typical locations for metastatic disease include lymph nodes and bone, in addition to lungs and liver.

TABLE 36.3 Hereditary Syndromes Associated With Adrenocortical Carcinomas and Pheochromocytomas and/or Paragangliomas

ADRENOCORTICAL CARCINOMA (APPROXIMATELY 10% HEREDITARY)	PHEOCHROMOCYTOMA/PARAGANGLIOMA (APPROXIMATELY 30–40% HEREDITARY)
Li-Fraumeni (*TP53* gene)	Multiple endocrine neoplasia type 2 (*RET* gene)
Lynch syndrome (MMR genes)	*VHL* syndrome
MEN1	*NF1*
Beckwith-Wiedemann syndrome	Hereditary Paraganglioma-Pheochromocytoma syndromes (*SDHx, MAX, TMEM127*)
Familial adenomatous polyposis (*APC*)	Hereditary leiomyomatosis and renal cell carcinoma syndrome (*FH*)

MEN1, Multiple endocrine neoplasia 1; *NF1*, neurofibromatosis 1; *VHL,* Von Hippel-Lindau.

22. What clues suggest that a primary pheochromocytoma is at higher risk of becoming metastatic in the future?

The clinical or histological features of the primary pheochromocytoma cannot predict future distant metastases, although there is a higher risk with tumors larger than 4–5 cm, tumors that result from germline pathogenic variants in *SDHB*, tumors with high dopamine or methoxytyramine secretion, and perhaps tumors with a high Ki67 index. There are histopathologic scoring systems but they have high inter- and intra-observer variability and, therefore, are not very reliable.

23. Which of the familial pheochromocytoma/paraganglioma syndromes is most commonly associated with metastatic disease?

Table 36.3 lists the well-recognized familial pheochromocytoma and paraganglioma syndromes. *SDHB* germline pathogenic variants associated with pheochromocytomas and paragangliomas portend the highest risk of developing metastatic disease (25–50%). *SDHA*–associated pheochromocytomas and paragangliomas are quite rare but also have a higher rate of developing metastatic disease (12%). Of note, about half of those patients with metastatic pheochromocytomas and paragangliomas have sporadic disease (no known germline pathogenic variant).

24. What are the best tests to localize metastatic pheochromocytomas and paragangliomas?

Cross-sectional imaging with CT or MRI will localize most metastatic pheochromocytomas and paragangliomas and is the initial imaging procedure of choice in most circumstances due to cost. However, functional imaging with somatostatin receptor-based imaging [68-Ga DOTATATE PET/CT] is the most sensitive to pick up all sites of metastatic disease, especially bony disease. DOTATATE PET/CT has been shown to be superior to and to have largely replaced 123-I-metaiodobenzylguanidine (MIBG) scans, which have low sensitivity for metastatic disease. One study showed a better metastatic lesion detection rate with 68-Ga Dotatate PET/CT (97.6%) compared with CT/MRI (81.6%), 18F-FDG PET/CT (77.7%), 18F-FDOPA PET/CT (74.8%), and 18F-FDG PET/CT (49.2%). Therefore, 68-Ga DOTATATE PET/CT is currently the most accurate imaging technique available for the detection of metastatic pheochromocytomas and paragangliomas.

25. What is the treatment for metastatic pheochromocytomas and paragangliomas?

Surgery is the treatment of choice, when possible, especially to debulk highly secretory disease. Preoperatively, alpha-adrenergic blocking agents (phenoxybenzamine, prazosin, terazosin, doxazosin) or calcium channel blockers are given to control blood pressure. Fluids and salt are given to replete intravascular volume. Beta-blockers may then be added for reflex tachycardia from a good alpha blockade.

There are no curative therapies for metastatic pheochromocytoma and paraganglioma. The goal is often to control disease and biochemical secretion. Therapies associated with partial tumor responses include chemotherapy with cyclophosphamide, vincristine, and dacarbazine, and radionuclide therapy with ^{131}I-MIBG. Peptide receptor radionuclide therapy (PRRT) using^{177} Lu-DOTATATE has also shown promising retrospective results in subsets of patients. Similarly

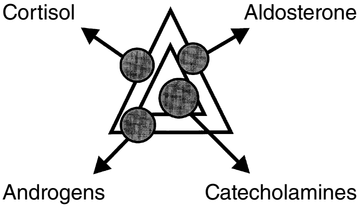

Figure 18.1

encouraging responses have also been recently reported with tyrosine kinase inhibitors such as sunitinib and cabozantinib. There are ongoing clinical trials with other targeted agents. These therapies can also help biochemical control, in addition to using alpha-blockers, calcium channel blockers, and a tyrosine hydroxylase inhibitor (metyrosine) for blood pressure control. High catecholamines can also cause severe functional ileus, so a strong bowel regimen should be given.

26. What is the prognosis for metastatic pheochromocytomas and paragangliomas?

The 5-year survival rate is approximately 50–69%. One study reported a mean overall survival of 24.6 years and a mean disease-specific survival of 33.7 years. Shorter survival was predicted with male gender, older age, large primary tumor size, synchronous metastases at diagnosis, elevated dopamine levels, and not undergoing primary tumor resection. Some patients have metastases that are stable for over 40 years and others have metastases discovered >50 years after the primary diagnosis was made. Therefore, pheochromocytomas and paragangliomas require lifelong surveillance, and metastatic pheochromocytomas and paragangliomas are managed much like any other chronic illness, with attention focused on controlling blood pressure and symptoms of catecholamine excess.

27. What tumors metastasize to the adrenal glands and what are other noncortical adrenal tumors?

The highly vascular adrenal glands are a frequent site of bilateral metastatic spread from cancers of the lung, breast, stomach, colon, liver, and kidney, and from melanomas. The differential diagnosis for primary nonadrenocortical tumors also includes lymphoma, angiomyolipoma, malignant epithelial carcinoma, epithelioid angiosarcoma, and neurinoma.

28. What is the clinical significance of metastatic disease to the adrenal glands?

Acute adrenal crises from metastases to the adrenal glands are rare. However, up to 33% of patients may have subtle adrenal insufficiency manifested by nonspecific symptoms and an inadequate response to a 250-mcg cosyntropin stimulation test (peak cortisol level <18 mcg/dL). These patients may experience improvement in well-being when given physiologic glucocorticoid replacement.

KEY POINTS

- Adrenocortical carcinomas present with features of excess cortisol, androgens, aldosterone, or estrogens; with abdominal or flank pain; or as an incidentally discovered adrenal mass.
- Metastatic pheochromocytomas often present with clinical features similar to those of localized pheochromocytomas (hypertension, headaches, palpitations, and sweating).
- Features suggesting that an adrenal tumor is malignant are size >4 cm, heterogeneity, calcifications, irregular borders, local invasion, lymphadenopathy, decreased lipid content (Hounsfield units [HU] >20), or elevated levels of serum cortisol and androgens on urinary or plasma evaluation.
- Surgery is the treatment of choice for all malignant adrenal tumors; mitotane +/– chemotherapy and tumor bed radiation therapy are recommended adjuvant therapies for adrenocortical carcinomas.

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Adrenal Insufficiency*

Cecilia C. Low Wang and Ethan Stortz

1. What is adrenal insufficiency, and how is it categorized?

Adrenal insufficiency refers to inadequate production of glucocorticoids and/or mineralocorticoids by the adrenal glands. Destruction or dysfunction of the adrenal cortex itself causes primary adrenal insufficiency. Secondary adrenal insufficiency results from inadequate adrenocorticotropic hormone (ACTH) production by the pituitary gland, while inadequate corticotropin–releasing hormone (CRH) production by the hypothalamus defines tertiary adrenal insufficiency.

2. What are the common causes of adrenal insufficiency?

Autoimmune adrenalitis (Addison's disease) is the most common cause of primary adrenal insufficiency and is associated with increased levels of 21-hydroxylase antibodies. Addison's disease can occur in isolation or in combination with other endocrine deficiencies as part of an autoimmune polyglandular syndrome. The most common cause of central (i.e., secondary/tertiary) adrenal insufficiency is the withdrawal of glucocorticoids after long-term use. Central adrenal insufficiency can also occur as the result of large pituitary tumors or their treatment with surgery and/or radiation therapy. See Table 37.1 for other causes of adrenal insufficiency.

3. When can glucocorticoid therapy cause adrenal insufficiency?

While any supraphysiologic dose of glucocorticoid can suppress the hypothalamic-pituitary-adrenal (HPA) axis, the risk of adrenal insufficiency increases with the dose and duration of systemic glucocorticoid therapy. Treatment with prednisone ≥5 mg daily for >4 weeks, prednisone 20 mg for >2 weeks, high-potency or long-acting agents, or evening/nighttime glucocorticoid administration increases the risk of adrenal insufficiency. Short courses, infrequent regimens (<14 days), and daytime or alternating-day administration of systemic glucocorticoids can decrease this risk. Aside from systemic steroids, inhaled corticosteroids present the next highest risk of developing adrenal insufficiency, especially when fluticasone propionate is used (high-affinity and long-acting) or when any agent is used longer than 6–12 months. While rarer cases of adrenal insufficiency have been reported with joint/bursa glucocorticoid injections as well as topical corticosteroid preparations.

4. What are the common symptoms of adrenal insufficiency?

Most patients report nonspecific symptoms such as weakness, fatigue, and anorexia. Gastrointestinal symptoms are also common, such as nausea, vomiting, vague abdominal pain, or constipation. Some patients report lightheadedness, arthralgias, myalgias, amenorrhea, depression, psychosis, or memory issues.

5. How does primary adrenal insufficiency differ from secondary/tertiary adrenal insufficiency?

Key differences in clinical signs between primary and secondary/tertiary adrenal insufficiency include hyperpigmentation and hypokalemia in primary adrenal insufficiency. Hyperpigmentation of the buccal mucosa, gums, palmar creases, nail beds, and recent scars occur due to proopiomelanocortin (POMC) production. POMC is a prohormone that is cleaved into ACTH, melanocyte-stimulating hormone (MSH), and other hormones, which leads to increased melanin production. See Table 37.2 for more detail.

6. What causes the laboratory abnormalities found in adrenal insufficiency?

Hyperkalemia is seen only in primary adrenal insufficiency while hyponatremia can be seen in both primary and secondary/tertiary adrenal insufficiency. Hyperkalemia is due to

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*Emily Schroeder, MD, co-authored and edited previous versions of this chapter.

TABLE 37.1 Causes of Adrenal Insufficiency*

	PRIMARY	SECONDARY	TERTIARY
Autoimmune	Addison disease	Lymphocytic hypophysitis	
Infiltrative	Amyloidosis Histiocytosis Sarcoidosis	Amyloidosis Hemochromatosis Histiocytosis IgG4–related disease Sarcoidosis	Hemochromatosis Histiocytosis Sarcoidosis
Tumor	Bilateral primary adrenal tumors Lymphoma Bilateral metastases	Pituitary adenoma/carcinoma Craniopharyngioma Germinoma Lymphoma Meningioma Metastases (breast, lung, colon, prostate) Other CNS tumors	Craniopharyngioma Glioma Metastases Sellar masses extending into the hypothalamus Other CNS tumors
Infection	CMV HIV Histoplasmosis PJP TB Bacterial (*E. coli, H. influenzae, GAS, Legionella N meningitidis, P aeruginosa*, *S. pneumoniae,* & others)	*Actinomyces* Histoplasmosis HIV Syphilis TB	Infectious encephalitis Meningitis TB
Vascular	Bilateral adrenal hemorrhage (Waterhouse-Friederichson Syndrome): bacterial infection, DIC, sepsis, shock APLS Other vasculitis	Aneurysm Apoplexy (Sheehan's syndrome) Subarachnoid hemorrhage	Hypothalamic hemorrhage Subarachnoid hemorrhage
Genetic	Adrenal hypoplasia congenita Adrenoleukodystrophy APS1 CAH	POMC mutations Pituitary transcription factor mutations	
Iatrogenic	Bilateral adrenalectomy	Pituitary surgery Pituitary radiation TBI	Radiation TBI
Medications	Adrenolytic medications Checkpoint inhibitors CYP3A4 inducers Inhibitors of steroidogenesis enzymes	Checkpoint inhibitors Opioids	Glucocorticoids Opioids

*This table is not exhaustive.

Adapted from Hahner S, Ross RJ, Arlt W, et al. Adrenal insufficiency. *Nat Rev Dis Primers*. 2021;7(1):19 and Husebye ES, Castinetti F, Criseno S, et al. Endocrine–related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. *Eur J Endocrinol.* 2022;187(6):G1–G21.

APLS, antiphospholipid antibody syndrome; *APS1*, autoimmune polyglandular syndrome type 1; *CAH*, congenital adrenal hyperplasia; *CMV*, cytomegalovirus; *DIC*, disseminated intravascular coagulation; *CNS*, central nervous system; *GAS*, Group A *Streptococcus; HIV* human immunodeficiency virus; *PJP*, *Pneumocystis jiroveci; POMC*, pro-opiomelanocortin; *TB*, *Mycobacterium tuberculosis; TBI*, traumatic brain injury.

mineralocorticoid deficiency, whereas the causes of hyponatremia are multifactorial: both mineralocorticoid and glucocorticoid deficiency can result in lower effective circulating volume leading to vasopressin release. Loss of cortisol also results in decreased inhibition of vasopressin release, causing higher vasopressin levels and increased aquaporin 2 expression in the renal collecting ducts. Sodium wasting from mineralocorticoid loss in primary adrenal insufficiency also contributes to hyponatremia. Azotemia can be seen because of hypovolemia while hyperchloremic/

TABLE 37.2 A Comparison of Primary and Secondary/Tertiary Adrenal insufficiency

	Primary AI	***Secondary/Tertiary AI***
PRIMARY DYSREGULATION	**↓ CORTISOL** **↓ ALDOSTERONE**	**↓ ACTH AND/OR ↓ CRH**
Hormonal Changes		
Adrenal	↓ cortisol ↓ aldosterone	↓ cortisol
Pituitary	↑ ACTH	↓ ACTH
Hypothalamic	↑ CRH	↓ CRH if tertiary
Symptoms		
Hyperpigmentation	Yes	No
Salt-craving	Yes	No
Fatigue, anorexia, nausea, vomiting, abdominal pain	Yes	Yes; nausea/vomiting less common
Orthostatic hypotension, dizziness	Yes	Yes, but less often
Adrenal crisis	Yes	Yes, but less often
Signs		
Hypotension	Yes	Yes, but less often
Hyponatremia	Yes	Yes
Hyperkalemia	Yes	No
Hypercalcemia	Yes	Possible, but rare
Nonanion gap metabolic acidosis	Yes	No
Azotemia	Yes	Yes
Hypoglycemia	Yes, but less often	Yes
Anemia	Yes	No
Eosinophilia	Yes	Yes

ACTH, adrenocorticotropin hormone; *AI,* adrenal insufficiency; *CRH,* corticotropin–releasing hormone.

nonanion gap metabolic acidosis can be seen with aldosterone deficiency. Patients with primary adrenal insufficiency often develop anemia due to concurrent pernicious anemia or decreased red cell mass for which the mechanism is unclear. Eosinophilia can be seen in either primary or secondary/tertiary adrenal insufficiency. Mild to moderate hypercalcemia may occur and is thought to be due to volume depletion and decreased calcium filtration through the glomerulus. It's possible that intestinal calcium absorption is enhanced, and/or bony stores increase calcium release. Fasting blood glucose is usually low-normal, but occasionally patients can develop fasting or postprandial hypoglycemia. This is likely due to increased insulin sensitivity from cortisol deficiency and decreased counter regulatory action of cortisol. Patients with coexisting type 1 diabetes mellitus and adrenal insufficiency may develop increased frequency and severity of hypoglycemic episodes.

7. How is adrenal insufficiency diagnosed biochemically?

In the outpatient setting, a low morning cortisol (<3 µg/dL) is sufficient to diagnose adrenal insufficiency so long as the patient has not taken exogenous glucocorticoids in the preceding 24 hours. A high morning cortisol (>18 µg/dL on traditional/older assays) excludes the diagnosis. Levels between 3 and 18 ug/dL usually require dynamic testing, such as the cosyntropin stimulation test, for diagnosis.

The standard cosyntropin stimulation test determines whether the adrenal glands are able to respond to maximal stimulation by synthetic ACTH. The test can also be used in the diagnosis

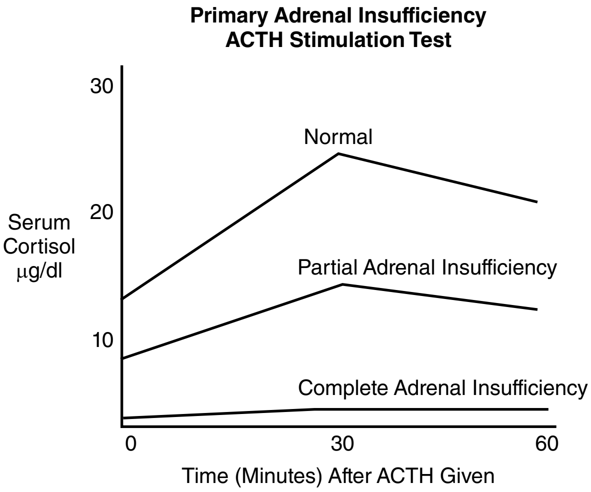

Fig. 37.1 Interpretation of the ACTH stimulation test.

of central adrenal insufficiency as long as sufficient time (estimate ≥2 weeks) has elapsed for the adrenal cortex to atrophy in response to lack of ACTH stimulation. Otherwise, the results of stimulation testing in this setting will be falsely normal (see #11).

The standard cosyntropin test is performed by drawing a baseline serum cortisol level, administering 250 µg of cosyntropin (brand names Cortrosyn or Synthacthen) intravenously (IV) or intramuscularly (IM), then drawing a serum cortisol level 30 and 60 minutes later. An abnormal result is defined as a stimulated cortisol of <18–20 µg/dL on traditional/older assays (<500–550 nmol/L) at either 30 or 60 minutes. This test can be performed at any time of day. If an individual is receiving glucocorticoid therapy, the dose should be held before the test is performed (12 hours for hydrocortisone, 24 hours for prednisone) to avoid detecting synthetic glucocorticoids in the cortisol assay. See Fig. 37.1.

Older cortisol immunoassays had cross-reactivity with other endogenous steroids. New-generation immunoassays and liquid chromatography-mass spectrometry (LC-MS) assays are more specific for cortisol, so the cutoff for a normal morning or post-cosyntropin cortisol may be closer to 12–15 µg/dL (350–415 nmol/L).

Other dynamic tests include the insulin tolerance test, metyrapone test, glucagon stimulation test, and CRH stimulation test. The insulin tolerance test evaluates the HPA axis in response to insulin-induced hypoglycemia (blood glucose of <40 mg/dL). This test should only be performed in experienced centers with trained staff and should not be performed if the individual has significant coronary artery disease or an uncontrolled seizure disorder. Metyrapone blocks the final step in cortisol biosynthesis, which decreases cortisol levels and increases ACTH secretion.

8. What is the role of the low-dose cosyntropin stimulation test?

Some clinicians argue that the standard-dose cosyntropin stimulation test may miss mild cases of primary adrenal insufficiency due to the dose of ACTH administered in this test, which is quite supraphysiologic. Data from studies examining the administration of 1 µg cosyntropin instead of the usual 250 µg do not clearly establish that the low-dose test is better than the standard test. There are several potential problems with performing this low-dose test, including false-positive testing as a result of inaccurate or inconsistent dilution of cosyntropin, the need for IV administration, and the need for carefully timed sampling for serum cortisol levels. It is unclear whether abnormal results from this test are clinically relevant. Therefore, the standard dose test should be used in most instances.

9. What are some pitfalls in cortisol testing?

Around 10% of cortisol is freely circulating and biologically active. Approximately 70–80% of cortisol is bound to corticosteroid-binding globulin (CBG) while 10–20% is bound to albumin.

Cortisol LC-MS and immunoassays measure both free and bound cortisol. Clinical states altering CBG and albumin concentrations can alter total cortisol values and lead to false-positive or false-negative testing for adrenal insufficiency. Both high estrogen states (such as pregnancy and contraceptive pill use) and mitotane use increase CBG levels. Critical illness, inflammation, and cirrhosis lead to decreased CBG and albumin levels, making adrenal insufficiency testing difficult in these populations.

In cases of hypoalbuminemia, some authors have proposed using albumin as a surrogate marker for CBG. However, the correlation of CBG to albumin in cirrhosis or critical illness is weak. Others have proposed the use of free cortisol. A cutoff of 0.9 μg/dL had high sensitivity and specificity in healthy volunteers for predicting morning cortisol <18 μg/dL, and another study showed that a peak free cortisol <0.9 μg/dL after standard cosyntropin stimulation testing had high sensitivity and specificity for diagnosing adrenal insufficiency in patients with mild cirrhosis. Importantly, free cortisol testing is not widely available and requires more extensive study before its use in clinical testing can be recommended.

10. What testing can be used to distinguish primary from central adrenal insufficiency?

In primary adrenal insufficiency, plasma ACTH is elevated, whereas ACTH is low or "abnormally normal" (i.e., not elevated in response to low cortisol) in secondary/tertiary adrenal insufficiency.

11. When can the results of the ACTH stimulation test be misleading?

Partial ACTH deficiency and recent ACTH deficiency are situations that may lead to false-negative results of the cosyntropin stimulation test. Insulin-induced hypoglycemia (i.e., insulin tolerance testing) or metyrapone testing may be used in these situations. CRH stimulation testing can also be done, but this compound is not available in the United States.

Corticosteroid joint injections can cause an abnormal response to cosyntropin stimulation testing, and it may take several weeks for HPA function to normalize. During HPA-axis recovery, ACTH levels remain elevated as the adrenal glands slowly increase cortisol production.

12. What role does DHEA-S testing have in adrenal insufficiency?

Dehydroepiandrosterone sulfate (DHEA-S) is an adrenal androgen responsive to ACTH and has a half-life of 7–10 hours. Some authors suggest that a cut-off of >54.5 μg/dL makes adrenal insufficiency unlikely, though more standard tests are still required to formally diagnose adrenal insufficiency.

13. When are imaging tests appropriate?

After the biochemical diagnosis of adrenal insufficiency, imaging tests can help determine the cause in certain instances. For secondary/tertiary adrenal insufficiency, magnetic resonance imaging (MRI) of the pituitary and hypothalamus is indicated if exogenous glucocorticoid use has been ruled out. If a primary adrenal process is suspected, an abdominal computed tomography (CT) scan can be performed with thin cuts through the adrenal glands. Imaging should not be performed before a biochemical diagnosis is made because of the high incidence of incidental findings without clinical significance. As a general rule, bilateral small glands are usually seen in patients who have autoimmune adrenalitis (Addison's disease), while large adrenal glands are found in most other causes of primary adrenal insufficiency.

14. Develop an algorithm for the evaluation of adrenal insufficiency.

See Fig. 37.2.

15. What constitutes an adrenal crisis?

Adrenal crisis is more common in primary than secondary/tertiary adrenal insufficiency and should be suspected in patients with unexplained catecholamine-resistant hypotension.

Patients must meet two or more of the following criteria:

- Hypotension or hypovolemic shock
- GI symptoms: nausea or vomiting
- Severe fatigue
- Fever
- Encephalopathy: drowsiness, lethargy, confusion, delirium, seizure, or coma

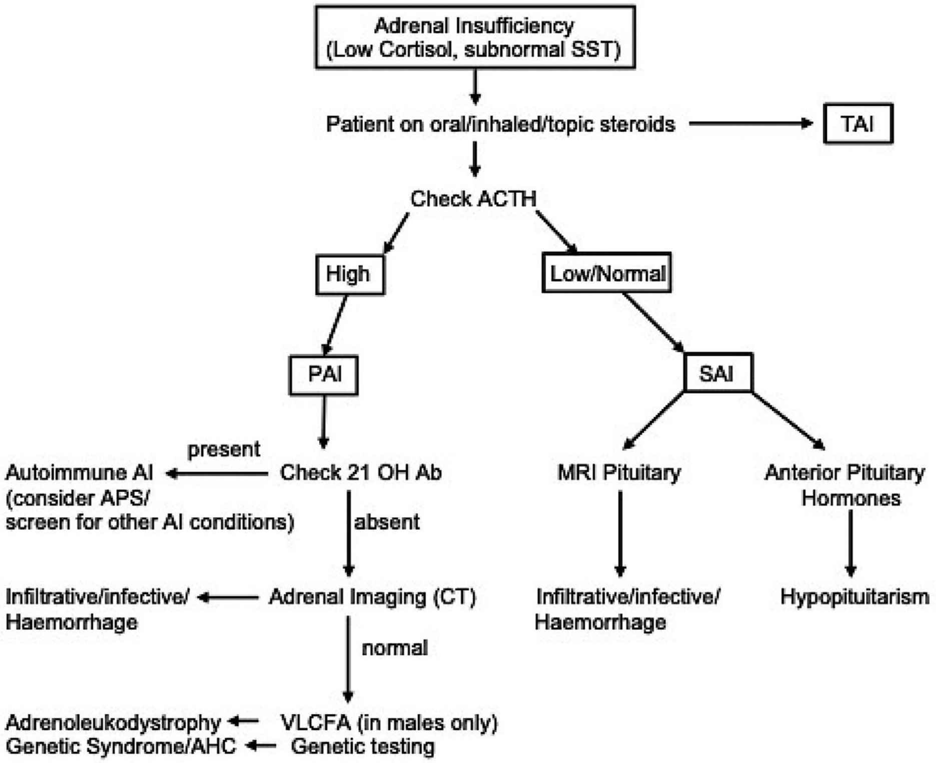
Adrenal Insufficiency
(Low Cortisol, subnormal SST)
Patient on oral/inhaled/topic steroids
TAI
Check ACTH
High
Low/Normal
PAI
SAI
present
Autoimmune AI
(consider APS/
screen for other AI conditions)
Check 21 OH Ab
absent
MRI Pituitary
Anterior Pituitary
Hormones
Infiltrative/infective/
Haemorrhage
Adrenal Imaging (CT)
Infiltrative/infective/
Haemorrhage
Hypopituitarism
normal
Adrenoleukodystrophy
Genetic Syndrome/AHC
VLCFA (in males only)
Genetic testing

Fig. 37.2 Evaluating the cause of adrenal insufficiency. (Adapted from Kumar R, Wassif WS. Adrenal insufficiency. *J Clin Pathol.* 2022;75(7):435–442. AI, adrenal insufficiency. VLCFA, a very long-chain fatty acid.)

TABLE 37.3 Treatment of Adrenal Crisis

Primary Adrenal Insufficiency
Treatment of Adrenal Crisis

AGENT	DOSE
Hydrocortisone (Solu-Cortef)	100 mg IV, then 200 mg/24-hr infusion × 24 hour, then 100 mg/24 hr infusion × 24 hr
Normal Saline (+/– D5)	1 L over 1 hour, then guided by individual needs

IV, intravenous; D5 (5% Dextrose solution)
Adapted from Bornstein SR, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101(2):364–89, with permission. © Endocrine Society.

Common lab abnormalities in adrenal crisis include hyponatremia, hypoglycemia, lymphocytosis, and eosinophilia. Crises are often triggered by acute illness, infection, trauma, severe pain, intense stress, strenuous exercise, rapid changes in glucocorticoid doses, surgical procedures, or pregnancy labor.

16. How is an adrenal crisis managed?

Adrenal crisis is often fatal and should be treated aggressively when suspected. A formal diagnosis of adrenal insufficiency can be performed later. Empiric treatment with IV hydrocortisone should be initiated (see Table 37.3). Alternatively, a single dose of dexamethasone 4 mg IV can be given while baseline cortisol and cosyntropin stimulation testing are performed before hydrocortisone is initiated, since dexamethasone is not detected in standard serum cortisol assays. Treatment should include intravenous saline and glucose to correct volume depletion, dehydration, and hypoglycemia. Patients often need supportive care in an intensive care setting. A search for precipitating factors and the underlying cause is required.

17. How is adrenal insufficiency diagnosed in the critical care setting?

Patients who are hemodynamically unstable and unresponsive to vasopressors despite adequate fluid resuscitation or who have signs/symptoms suggestive of adrenal insufficiency should have a random cortisol level drawn. Disruption of the diurnal rhythm of ACTH and cortisol secretion in acute illness and severe stress should stimulate cortisol production, so a low or "low for the clinical state" random cortisol is consistent with complete or relative adrenal insufficiency in the critical care setting. A cosyntropin stimulation test can be considered, but the benefits of formal testing for adrenal insufficiency in critically ill patients continue to be debated.

The cortisol level at which adrenal insufficiency should be diagnosed in critical illness is controversial. Random cortisol levels of <15 µg/dL (or <10 µg/dL if albumin is <2.5 g/dL), < 20 µg/dL, or <25 µg/dL have all been proposed as cutoffs for relative adrenal insufficiency in critical illness. Others have suggested a cortisol change (previously referred to as "cortisol delta" of <9 µg/dL after cosyntropin administration) may be more suggestive of adrenal insufficiency. Inflammatory cytokines and proinflammatory transcription factors may cause reduced corticosteroid-binding globulin (CBG), decreased CBG-binding affinity, cortisol resistance, or increased cortisol metabolism, making it difficult to know what level of plasma cortisol is physiologically appropriate. Some clinicians believe that a cortisol level that is considered normal in an ambulatory environment may not be adequate in the setting of severe stress, critical illness, or complicated surgical procedures. This proposed pathophysiology is referred to as relative adrenal insufficiency, functional adrenal insufficiency, or critical illness–related corticosteroid insufficiency.

18. When and how should glucocorticoids be used in the critical care setting?

There is considerable debate regarding the appropriate use of glucocorticoids in the critical care setting. Trials of glucocorticoid therapy for sepsis in patients without proven adrenal insufficiency have shown mixed results. One systematic review of 33 trials showed that treatment with glucocorticoids in sepsis reduced 28-day mortality and increased the resolution of shock. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial empirically treated individuals with severe sepsis with hydrocortisone and found faster resolution of shock but no change in overall mortality. In contrast, the Recombinant Human Activated Protein C and Low Dose of Hydrocortisone and Fludrocortisone in Adult Septic Shock (APROCCHSS) trial did find a mortality benefit from the use of hydrocortisone plus fludrocortisone.

Most groups advocate for treating septic shock unresponsive to adequate fluid resuscitation and vasopressor therapy with hydrocortisone at doses of 200–300 mg/day (50 mg IV every 6 hours or 100 mg IV every 6 hours). These doses should be tapered quickly as the patient's clinical status improves and the underlying illness resolves.

19. How do I manage chronic adrenal insufficiency, and when should I consider prescribing fludrocortisone?

All patients with chronic adrenal insufficiency require replacement with glucocorticoids. Hydrocortisone is frequently used in primary adrenal insufficiency because it has some mineralocorticoid activity and can be dosed in a way that mimics the normal diurnal variation of serum cortisol levels. The usual dosage of hydrocortisone is 10–15 mg every morning and 5–10 mg in the afternoon. The hydrocortisone total daily dose can be tailored to body surface area, with an estimated requirement of 7–12 mg/m^2/day. When prednisone is used, typical doses are 2.5–5 mg daily.

Mineralocorticoid replacement is recommended for all individuals with primary adrenal insufficiency. Fludrocortisone 0.05–0.2 mg daily can be added and adjusted for blood pressure, orthostatic hypotension, salt cravings, and hyperkalemia. The dose should be titrated based on these clinical parameters, but plasma renin levels can also be used to guide therapy. Goal plasma renin activity for these patients is in the upper half of the reference range.

20. What deficiencies exist in the current approach to treating adrenal insufficiency?

Many individuals with adrenal insufficiency experience significantly reduced quality of life, diminished health status, increased fatigue, and higher rates of depression. This may be at least

TABLE 37.4 Relative Potencies of Selected Steroid Formulations

COMPOUND	PHYSIOLOGIC REPLACEMENT DOSE, MG	GLUCOCORTICOID ACTIVITY[**] RELATIVE TO HYDROCORTISONE	MINERALOCORTICOID ACTIVITY RELATIVE TO HYDROCORTISONE	DURATION OF ACTION
Hydrocortisone[*]	20	1	1.0	(8–12 hrs.)
Methylprednisolone	4	4	0.5	(12–36 hrs.)
Prednisone	5	4	0.75	(12–36 hrs.)
Prednisolone	5	4	0.75	(12–36 hrs.)
Dexamethasone	0.50	17	0.0	(36–72 hrs.)
Fludrocortisone	0–15	10–15	125	(12–36 hrs.)

[*] Hydrocortisone is the synthetic form of cortisol.
[**] Suppression of hypothalamic-pituitary-adrenal axis

partially attributable to glucocorticoid replacement regimens that do not replicate the physiological diurnal cortisol profile. Additionally, most female patients do not receive adrenal androgen replacement. Sustained–release glucocorticoid formulations that better approximate the natural diurnal cortisol patterns are being developed. Two such preparations are available in Europe, marketed under the trade names Plenadren and Efmody.

21. Should I recommend dehydroepiandrosterone replacement for my adrenally insufficient patient?

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are the primary androgens produced by the adrenal glands. Both are weak androgens that are peripherally converted to the more potent androgens testosterone and 5α-dihydrotestosterone (DHT). This peripheral conversion is a significant source of androgens in women. Oral DHEA supplementation with 25–50 mg/day normalizes circulating levels of androgens in women with primary adrenal insufficiency. A meta-analysis of 10 randomized, placebo-controlled trials showed a small improvement in health–related quality of life and depression after treatment with DHEA with no significant improvement in anxiety or sexual well-being. These data are insufficient to recommend DHEA therapy for all women with adrenal insufficiency, but it may be tried in women who continue to have significantly impaired well-being despite optimal glucocorticoid and mineralocorticoid treatment. In the United States, DHEA is classified as a dietary supplement and is therefore not subject to the same quality control as medications.

22. What are the relative potencies of available glucocorticoids?

See Table 37.4.

23. How is treatment for chronic adrenal insufficiency monitored?

Adequate treatment for chronic adrenal insufficiency requires monitoring of clinical status, such as weight, blood pressure, orthostasis, and electrolytes as well as overall well-being. It is important to avoid supraphysiologic doses of replacement glucocorticoids. Overreplacement can lead to iatrogenic Cushing's syndrome, resulting in weight gain, hypertension, hyperglycemia/diabetes, glaucoma, osteoporosis, avascular necrosis, and increased risk of infection. The goal of steroid replacement is to use the lowest glucocorticoid (and mineralocorticoid) doses possible while maintaining normal electrolytes and a good quality of life. Serum cortisol and plasma ACTH levels are not useful for monitoring treatment, though a plasma renin level or activity can be helpful in titration of mineralocorticoid replacement, as described earlier in this chapter.

24. When do individuals with chronic adrenal insufficiency require "stress-dose" glucocorticoids, and what doses should be used?

Any medical stress including febrile illnesses, trauma, labor/delivery, and diagnostic or surgical procedures can precipitate an acute adrenal crisis in patients with chronic adrenal insufficiency.

TABLE 37.5 Stress Dosing of Glucocorticoids to Avoid an Adrenal Crisis.

Primary Adrenal Insufficiency
Prevention of Adrenal Crisis

CONDITION	SUGGESTED ACTION
Home Illness with Fever	T > 38 C (100.4°F) 2 × dose for 2–3 days T > 39 C (102.2°F) 3 × dose for 2–3 days
Same but No Oral Intake	Hydrocortisone 100 mg SQ or IM
Surgery: Minor/Moderate	Hydrocortisone 25–75 mg/24 hr
Surgery: Major, Trauma, Medical Intensive Care	Hydrocortisone 100 mg IV, then 50 mg every 6 hours IV or IM

IV, intravenous; *IM*, intramuscular; *SQ*, subcutaneous
Adapted from Bornstein SR, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2016;101(2):364–89, with permission. © Endocrine Society.

Supplemental steroids should be used to prevent an adrenal crisis while avoiding unnecessary additional doses. Typically, the usual replacement dose is doubled or tripled for mild-to-moderate infections and during labor and delivery. Doses should also be doubled or tripled for approximately 24 hours for dental surgeries, minor surgeries (cataract, laparoscopic, etc.), and invasive diagnostic procedures. Higher or true stress doses should be given in critical illness, significant traumatic injury, and major operations requiring general anesthesia. See Table 37.5.

25. What other precautions should individuals with adrenal insufficiency take?

Patients with adrenal insufficiency should wear a medical alert bracelet or necklace identifying them as individuals with adrenal insufficiency in case they encounter a medical emergency. Adrenal insufficiency should also be included in the "medical alert" information in the patient's smartphone. Intravenous, intramuscular, or rectal glucocorticoids can be administered in situations where an individual is unable to take medication by mouth.

26. What drugs can cause adrenal insufficiency?

The most common cause of secondary/tertiary adrenal insufficiency is glucocorticoid therapy. Glucocorticoids can cause exogenous Cushing's syndrome, leading to suppression of the HPA axis. Patients may develop overt adrenal insufficiency or fail to mount an adequate cortisol response to stress, predisposing them to an adrenal crisis if their steroid dose is abruptly stopped or tapered. High-dose progestins, such as megestrol and medroxyprogesterone acetate, can also cause exogenous Cushing's syndrome and HPA axis suppression, as these agents have significant glucocorticoid-receptor activity.

Protease inhibitors and other drugs that inhibit CYP3A4 slow the metabolism of glucocorticoids. When protease inhibitors and glucocorticoids are used together, they can cause exogenous Cushing's disease at low glucocorticoid doses.

Several drugs can cause primary adrenal sufficiency through interference with adrenal enzymes involved in steroidogenesis. These include azole antifungal agents, like ketoconazole, the paralytic agent etomidate, the antiparasitic drug suramin, aminoglutethimide, metyrapone, and mitotane. Osilodrostat, a 11β-hydroxylase and aldosterone synthase inhibitor, can cause adrenal insufficiency during medication titration, with continued use, and for a prolonged period after drug cessation. Some aldosterone synthase inhibitors may cause adrenal insufficiency given higher dosages could exhibit some 11β-hydroxylase inhibition, but this risk is thought to be low in newer, more specific aldosterone synthase inhibitors like baxdrostat.

Adrenal insufficiency has been described with abiraterone therapy for prostate cancer. Abiraterone, a 17α-hydroxylase (CYP17A1) inhibitor, is used to decrease androgen production. Blockade of this enzyme prevents the shift of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively. This results in decreased cortisol production. This alone does not cause adrenal insufficiency; corticosterone production is maintained (and even increased), and corticosterone can bind to the glucocorticoid receptor. The decrease in cortisol concentrations leads to less feedback on the hypothalamus and pituitary, so ACTH levels rise. This leads to increased production and accumulation of aldosterone and other mineralocorticoid precursors, leading to hypertension, hypokalemia, and fluid retention in some patients. For this reason, patients on abiraterone are usually given prednisone 5 mg twice daily (or sometimes 5 mg once daily). The ACTH-lowering effect of prednisone also decreases androgen production via the "backdoor pathway," an alternative process of dihydrotestosterone (DHT) production from steroid precursors other than DHEA, androstenedione, and testosterone. This chronic and generally supraphysiologic prednisone use is the culprit in adrenal insufficiency in patients treated with this agent.

Mifepristone, a progesterone antagonist at low doses, also causes adrenal insufficiency through antagonism of the glucocorticoid receptor at higher doses. This results in symptoms of adrenal insufficiency without concomitant low serum cortisol levels.

Opioids can significantly suppress the HPA axis and cause secondary/tertiary adrenal insufficiency predominantly through interactions at the mu-opioid receptor in the hypothalamus and pituitary gland. The risk of HPA axis suppression is thought to be related to dose and duration, but reduced levels of ACTH have been observed with acute administration of opioids. Estimates are inexact, but 10–35% of people on chronic opioid therapy may have adrenal insufficiency.

27. How do immune checkpoint inhibitors cause adrenal insufficiency?

Immune-checkpoint inhibitors (ICIs) can cause adrenal insufficiency in two ways: (1) hypophysitis, or pituitary gland inflammation, results in secondary/tertiary adrenal insufficiency (more common); (2) adrenalitis, or inflammation of the adrenal gland, causes primary adrenal insufficiency (more rare). Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) agents (ipilimumab) tend to cause hypophysitis up to 10% of the time. Abnormalities in multiple hormonal axes are common, and the median time to presentation is 9–12 weeks after therapy initiation. In contrast, antiprogrammed death protein 1 (PD-1) drugs (nivolumab, pembrolizumab) or antiprogrammed death ligand 1 (PD-L1) agents (atezolizumab, durvalumab) can cause hypophysitis or isolated secondary adrenal insufficiency through corticotroph cell toxicity in approximately 0.5–1% of cases, Median time to onset of adrenal insufficiency with these medications is approximately 26 weeks. Hypophysitis from ICI–related medications is almost always associated with adrenal insufficiency. Primary adrenal insufficiency from adrenalitis is rare. It tends to be associated with the use of PD-1/PD-L1 agents but is more common with a combination of CTLA-4 + PD-1/PD-L1 therapy.

Hypophysitis with CTLA-4 agents like ipilimumab usually causes headache, and diffuse pituitary and/or stalk enlargement is seen on MRI. Nivolumab-, pembrolizumab-, atezolizumab-, and other PD-1/PD-L1 agent–related hypophysitis is less often associated with headache, and MRI changes are evident in only about 28% of cases. Generally, adrenal insufficiency from hypophysitis is permanent, but axis recovery has been observed in up to 25% of cases. Recovery from ICI-induced adrenalitis/primary adrenal insufficiency does not occur.

Baseline cortisol and ACTH testing is recommended by some groups when immune-checkpoint inhibitor (ICI) therapy is initiated. Additionally, some professional societies recommend regular monitoring of morning cortisol ± ACTH levels throughout ICI therapy, though others feel that it is sufficient to proceed with testing only when patients exhibit signs or symptoms of adrenal insufficiency. Morning cortisol levels <5 μg/dL with low or inappropriately normal ACTH is suggestive of central adrenal insufficiency. Because ICI–related hypophysitis can occur rapidly, caution must be used when ordering and interpreting cosyntropin stimulation testing as the adrenal glands may not have had time to atrophy. Often, concurrent testing of TSH and free T4 can be helpful, as the coexistence of central hypothyroidism is suggestive of secondary adrenal insufficiency from hypophysitis. When primary adrenal insufficiency is suspected, 21-hydroxylase autoantibodies can be checked, although they are not present in all cases of ICI–related adrenalitis.

With regards to treatment, high-dose glucocorticoid therapy has not been shown to be helpful for either hypophysitis or adrenalitis, outside of the management of an adrenal crisis, optic chiasm compression, or other severe symptoms like extreme headache. Such treatment does not improve recovery of the HPA axis. Physiologic steroid replacement is recommended in all cases, regardless of etiology. Oftentimes, ICI therapy is continued despite the emergence of adrenal insufficiency, though it can be paused for moderate/severe symptoms or acute illness requiring hospitalization.

28. How should steroids be tapered in patients on pharmacologic doses of glucocorticoid to treat nonadrenal diseases?

Glucocorticoids are used to treat a variety of autoimmune, neoplastic, or other inflammatory disorders. Discontinuing glucocorticoid therapy can be challenging for multiple reasons:

1. The underlying disorder treated by the glucocorticoids may worsen.
2. Chronic suppression of the HPA axis may have caused secondary/tertiary adrenal insufficiency, and abrupt cessation could precipitate an adrenal crisis.
3. Even without adrenal insufficiency, patients may experience steroid withdrawal syndrome.

The initial tapering of glucocorticoids from pharmacologic to physiologic doses depends on the underlying condition for which the steroids are being used. If the disease worsens during this period of tapering, the dosage needs to be increased and continued until the symptoms stabilize before another attempt at more gradual tapering is made. When the patient is on a near-physiological glucocorticoid dosage, they can be switched to a shorter-acting agent such as hydrocortisone for continued taper below physiological dosages. Alternate-day therapy may be helpful in certain instances.

Testing should be performed when patients have been at or below physiologic doses for at least ≥1 month. A morning cortisol should be drawn ≥12 hours after hydrocortisone or ≥24 hours after longer-acting glucocorticoids like prednisone are held. A plasma cortisol level <10 μg/dL raises concern for adrenal insufficiency. When this happens, the glucocorticoid should be continued for 4–6 weeks before retesting. A level ≥10 μg/dL suggests the return of adrenal function, and the glucocorticoid can be stopped. Morning ACTH & DHEA-S levels can also be drawn with cortisol to get a sense of return of adrenal function. A cosyntropin stim test may be considered for cortisol levels between 5–15 μg/dL, keeping in mind that the result may be normal if the steroid-induced HPA suppression has not lasted long enough to cause adrenal atrophy. Of note, it may take months for the axis to respond normally to ACTH.

KEY POINTS

Classification and Diagnosis of Adrenal Insufficiency

1. Adrenal insufficiency is classified as primary (failure of adrenals to produce cortisol), secondary (failure of pituitary to produce ACTH), or tertiary (failure of hypothalamus to produce CRH).
2. Adrenal insufficiency should be suspected in outpatients who have received supraphysiologic doses of glucocorticoids for >1-month, intensive care unit (ICU) patients who are hemodynamically unstable despite aggressive fluid resuscitation or have septic shock, and any patient with signs or symptoms suggesting adrenal insufficiency.
3. Adrenal insufficiency is diagnosed using a 30- or 60-minute cortisol level <18 μg/dL in a standard-dose cosyntropin stimulation test, although new assays may list a cut-off of 12–15 μg/dL

KEY POINTS

Treatment of Adrenal Insufficiency

1. Treatment of adrenal insufficiency depends on the condition of the patient.
2. Nonstressed outpatients should be treated with replacement doses of hydrocortisone or prednisone with or without fludrocortisone, depending on the type of adrenal insufficiency.
3. Stressed patients should receive supplemental glucocorticoids tailored to the degree of stress.
4. The adrenal crisis should be treated aggressively using IV saline and dextrose, intravenous glucocorticoids (dexamethasone if treating before drawing random cortisol and ACTH, hydrocortisone afterward), other supportive care, and a search for the precipitating illness.

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CHAPTER 38

Congenital Adrenal Hyperplasia

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1. Define congenital adrenal hyperplasia.

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic disorders of the adrenal gland that lead to various defective steroidogenesis pathways for cortisol, aldosterone, and adrenal androgens. CAH results in increased levels of ACTH (corticotropin) and partial or complete defects of adrenal hormones with a variable phenotype based on the severity of the affected gene mutation.

2. How common is CAH?

The most common form of CAH, 21-hydroxylase deficiency, has an incidence of 1:14,000–1:18,000 births. The prevalence of this disorder varies greatly among different ethnic groups and is highest among the Ashkenazi Jewish population of Eastern Europe. The nonclassical form of 21-hydroxylase deficiency occurs in approximately 0.2% of the general Caucasian population but more frequently (1–2%) in Ashkenazi Jews. Because of its high prevalence, newborn screening for CAH is performed in most countries.

3. What is the normal steroidogenesis pathway in the adrenal cortex?

Six enzymes are required for the synthesis of cortisol from cholesterol in the adrenal cortex:

1. The **steroidogenic acute regulatory (StAR)** protein transports cholesterol to the mitochondria. This is the rate-limiting step in steroidogenesis.
2. The **P450 side-chain cleavage enzyme (CYP11A1)** is responsible for cholesterol side-chain cleavage to form progesterone.
3. **3β-hydroxysteroid dehydrogenase** converts the Δ5-steroids (pregnenolone, 17-hydroxypregnenolone, DHEA) to the Δ4-steroids (progesterone, 17-hydroxyprogesterone (17-OHP), androstenedione).
4. The three hydroxylases **CYP17A1 (17α -hydroxylase), CYP21A1 (21- hydroxylase)**, and **CYP11B1 (11β -hydroxylase)** convert specific precursors to steroids in the cortisol pathway.

Knowing this pathway (Fig. 38.1) is critical to recognizing and predicting the effects of each enzyme deficiency.

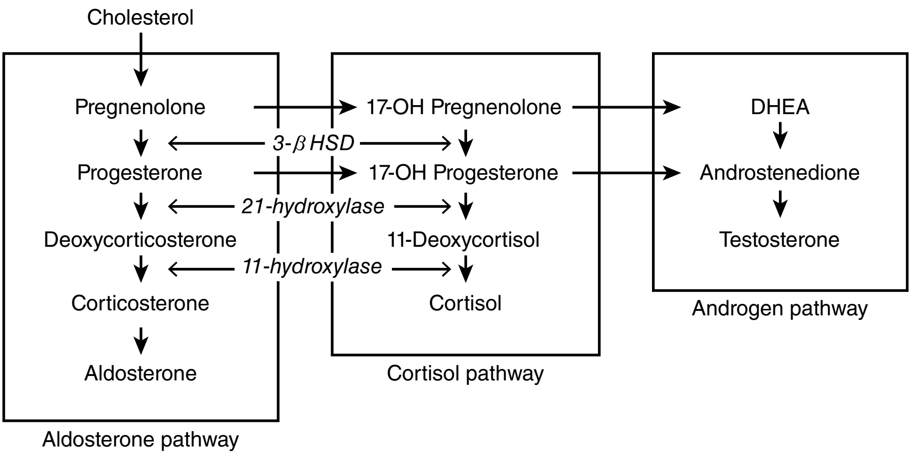
Cholesterol
Pregnenolone
17-OH Pregnenolone
DHEA
3-β HSD
Progesterone
17-OH Progesterone
Androstenedione
21-hydroxylase
Deoxycorticosterone
11-Deoxycortisol
Testosterone
11-hydroxylase
Corticosterone
Cortisol
Androgen pathway
Aldosterone
Cortisol pathway
Aldosterone pathway

Fig. 38.1 Steroidogenic pathway in the adrenal cortex. (*DHEA* = Dehydroepiandrosterone).

4. Explain why adrenal hyperplasia develops.

Adrenal hyperplasia results from elevated serum ACTH levels that stimulate the growth of the adrenal glands. This process begins *in utero* with reduced fetal cortisol production occurring due to decreased activity of one of the enzymes needed for cortisol synthesis. Cortisol normally acts through a negative feedback loop (Fig. 38.2) to inhibit ACTH secretion by the pituitary gland and corticotropin-releasing hormone (CRH) by the hypothalamus. The low serum cortisol levels in CAH result in increased CRH and ACTH secretion in an attempt to stimulate the adrenal glands to overcome the enzyme block and return the serum cortisol level to normal. Adrenal gland hyperplasia will occur as this process continues over time. Adrenal volume correlates positively with 17-OHP levels.

5. Describe the functions of the three hydroxylases.

- CYP17A1 (17α-hydroxylase) converts progesterone to 17-hydroxyprogesterone (17-OHP) and pregnenolone to 17-hydroxypregnenolone. This enzyme also includes a 17,20 lyase activity, which converts 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA).
- CYP21A2 (21-hydroxylase) converts progesterone to deoxycorticosterone (DOC) and 17-OHP to 11-deoxycortisol.
- CYP11B1 (11β-hydroxylase) converts DOC to corticosterone (which then is further metabolized to aldosterone) and 11-deoxycortisol to cortisol.

6. How is CAH inherited?

All of the enzyme defects leading to CAH are autosomal recessive disorders. Both copies of the involved gene must be abnormal for this condition to occur.

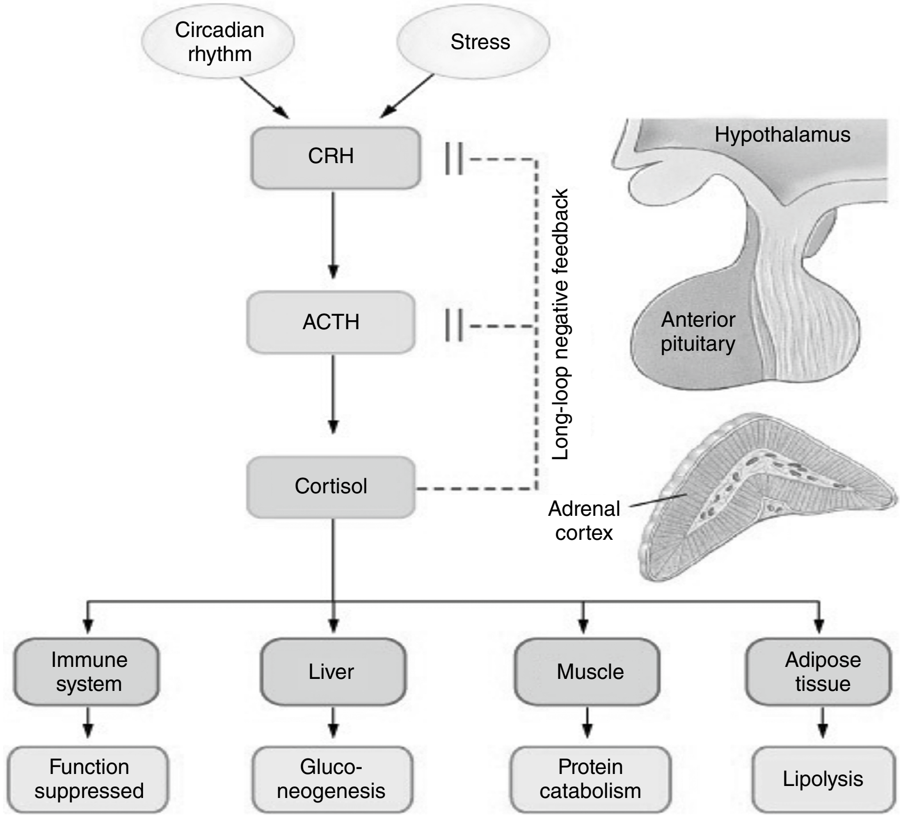
Circadian rhythm
Stress
CRH
ACTH
Cortisol
Long-loop negative feedback
Hypothalamus
Anterior pituitary
Adrenal cortex
Immune system
Liver
Muscle
Adipose tissue
Function suppressed
Gluco-neogenesis
Protein catabolism
Lipolysis

Fig. 38.2 Hypothalamic-pituitary adrenal axis and systemic effects of cortisol. *ACTH*, adrenocorticotropic hormone; *CRH*, cortocotropin-releasing hormone.

7. What is the most common form of CAH?

21-hydroxylase (CYP21A2) deficiency accounts for over 90% of CAH cases. This condition leads to severely reduced or absent CYP21A2 enzyme activity causing deficiencies of cortisol and the salt-retaining hormones, DOC and aldosterone, in both sexes, and/or virilization of genetic females. A major deficiency of CYP21A2 results in "classical" CAH.

8. Which genes encode for 21-hydroxylase?

Two genes encode for 21-hydroxylase: CYP21A1 (a pseudogene) and CYP21A2, both of which are located in a 35-kb region on the long arm of chromosome 6 (6p21.3), downstream of the gene coding for complement factor 4 (C4A and C4B). The CYP21A2 gene codes for the active 21-hydroxylase enzyme. CYP21A1 and CYP21A2 genes have 98% nucleotide sequence identity; however, the former has accumulated several mutations that inactivate its gene product.

9. What percentage of the population are heterozygote carriers of the 21-hydroxylase defect?

Less than 2% of the population are heterozygote carriers of the 21-hydroxylase defect. However, higher carrier rates of approximately 10% are observed in persons of European descent. Carriers have an abnormality in one of the two copies of the 21-hydroxylase gene and appear phenotypically normal, but may have an elevated 17-OHP after stimulation with exogenous adrenocorticotropic hormone (ACTH).

10. What causes most genetic events responsible for *CYP21A2* deficiencies?

Most of the genetic events responsible for CYP21A2 deficiencies result from the similarity between CYP21A1 and CYP21A2. This similarity leads to two types of recombination events between CYP21A2 and the pseudogene. 75% of events represent pseudogene mutations that are transferred to CYP21A2 during mitosis. This process is termed gene conversion. Twenty percent of events are meiotic recombinations producing a nonfunctional chimeric pseudogene. More than 60 additional mutations account for the remaining 5%.

11. What determines the patient's phenotype for 21-hydroxylase deficiency?

Clinical manifestations of the disease are related to the degree of cortisol deficiency and/or aldosterone deficiency, or accumulation of precursor hormones. More than 100 CYP21A2 mutations are known. The patient's phenotype is based on the specific alteration of the CYP21A2 gene and is grouped into three categories:

- Patients with no enzyme activity typically have large deletions or splicing mutations and predominantly have the salt-wasting form of CAH.
- Patients with a nonconservative amino substitution in exon 4 usually have 1%–2% enzyme activity and typically have the simple virilizing form of CAH.
- Patients with a point mutation in exon 7 have 20–50% of normal enzyme activity and most often have the nonclassical form of CAH.
- Patients who are heterozygotes have mild abnormalities but no clinically important endocrine disorders.

12. What is the second most common cause of CAH?

Seven percent of CAH cases are due to deficiency of the 11β-hydroxylase enzyme (CYP11B1). This is an autosomal recessive defect caused by a mutation on the short arm of chromosome 8 (8q24.3). 11β-Hydroxylase deficiency results in an increased level of DOC, which may cause hypertension through activation of the mineralocorticoid receptor leading to sodium retention and hypokalemic metabolic alkalosis. The enzyme deficiency also results in increased production of androgens and their precursors, which causes ambiguous genitalia in genetic females.

13. How common is 11β-hydroxylase deficiency?

11β-Hydroxylase deficiency is the second most frequent form of CAH. It occurs in 1:100,000 births in the general population but in 1:5,000 births in Jewish persons of Moroccan descent. CAH due to defects of the other enzymes listed here is extremely rare.

14. Summarize the rarer forms of CAH.

The rarer forms of CAH are 17α-hydroxylase and 3β-hydroxysteroid dehydrogenase deficiency. Fewer than 200 cases of 17α-hydroxylase deficiency are reported with 40 described mutations of CYP17 that span an 8.7-kb region on the short arm of chromosome 10 (10q24.3). The consequences of this deficiency are hypertension and hypokalemia due to DOC excess, associated with suppressed renin and aldosterone. Deficiency of androgens and androgen precursors also occurs, which causes pseudohermaphroditism in genetic males and delayed puberty in both sexes.

15. What are the clinical consequences of salt-wasting CAH?

Adrenal crisis in the newborn period is the most serious consequence of CAH. It usually occurs with genetic defects that result in severely reduced or absent enzyme activity, resulting in severely impaired production of both aldosterone and cortisol. It may be less obvious in genetic males who do not have ambiguous genitalia as a clue to the diagnosis. Overall, about two-thirds of patients with 21-hydroxylase deficiency have the salt-wasting form. These patients have decreased production of DOC and aldosterone, but increased levels of progesterone and 17-OHP which may act as mineralocorticoid antagonists that exacerbate the effects of aldosterone deficiency. Aldosterone deficiency leads to hypotension, volume depletion, hyponatremia, hyperkalemia, and increased renin activity. Cortisol deficiency contributes to poor cardiac function, poor vascular response to catecholamines, decreased glomerular filtration rate, and increased secretion of antidiuretic hormone. Both deficiencies lead to hyponatermia, dehydration, and shock.

16. What are other clinical consequences of CAH in females?

Androgen precursors are some of the metabolites that build up behind inhibited enzymes 21-hydroxylase, 11β-hydroxylase, and 3β-hydroxysteroid dehydrogenase. The following physical changes often result:

- Masculinization of the external genitalia of a genetic female fetus may lead to ambiguous genitalia at birth (female pseudohermaphroditism).
- Females may exhibit behaviors more typical of boys during childhood in terms of toy preference, rough play, and aggressiveness. However, most females with CAH are heterosexual and their sexual identity is female.
- Rapid growth during early childhood may occur with ultimate short stature as an adult due to early closure of epiphyses.
- Infertility is observed in approximately 20% of females with simple virilizing disease and 40% of females with salt-wasting disease.
- Osteopenia is observed in about 45% of young adult females with salt-wasting disease.
- Obesity is commonly seen in both sexes.
- Lower quality of life scores are reported by CAH patients compared to age- and sex-matched controls.
- Variable and subtle skin hyperpigmentation may occur.

17. What are other clinical consequences of CAH in males?

Newborn males with CAH due to deficiency of 21-hydroxylase or 11β-hydroxylase do not have ambiguous genitalia. Due to typical normal physical appearance, it is often difficult to detect an affected male, especially when symptoms of salt-wasting occur after the first week of life.

Later in childhood or early adulthood, males may present with the following:

- Premature puberty
- Variable and subtle hyperpigmentation
- Advanced height in early childhood with ultimate short stature
- Acne
- Testicular enlargement due to adrenal rest tumors, which may produce adrenal hormones
- Oligospermia and/or infertility
- Lower quality of life scores compared to aged- and sex-matched controls

18. Are patients with CAH at increased risk for cardiovascular disease?

Yes. Studies have demonstrated that patients with CAH have higher BMI, higher blood pressure, and more insulin resistance than age-matched controls. They demonstrate vascular endothelial dysfunction similar to other obese patients. These effects are especially prominent in males over 30 years of age.

19. How do patients with 17α-hydroxylase deficiency present?

In 17α-hydroxylase deficiency, the enzyme defect blocks the synthesis of androgens and leads to excess mineralocorticoids. Unlike in 21-hydroxylase deficiency, these patients do not develop adrenal crisis due to intact aldosterone synthesis. Patients present with:

- Cortisol deficiency
  - Adrenal Insufficiency
- Mineralocorticoid excess
  - Hypertension
  - Hypokalemia
- Androgen deficiency
  - Undervirilization in males
  - Absence of secondary sex characteristics and primary amenorrhea in females

20. How do patients with 11β-hydroxylase deficiency present?

In 11β-hydroxylase deficiency, the enzyme defect blocks the synthesis of aldosterone and cortisol. As such, these patients are at risk of adrenal insufficiency. They do not have a mineralocorticoid deficiency because they oversecrete the aldosterone precursor 11-deoxycorticosterone, which is a powerful mineralocorticoid. Excess precursors also drive the production of androgens and patients present with:

- Cortisol deficiency
  - Adrenal insufficiency
- Mineralocorticoid excess
  - Hypertension
  - Hypokalemia
- Androgen excess
  - Increased penile size in males
  - Ambiguous genitalia, including clitoral enlargement and labioscrotal fusion in females (female pseudohermaphroditism)

21. How do patients with 3β-hydroxysteroid dehydrogenase type 2 deficiency present?

In 3β-hydroxysteroid dehydrogenase type 2 deficiency, the enzyme defect blocks the synthesis of aldosterone, cortisol, and androgens. These patients are at risk of deficiency in all three pathways. However, in peripheral tissue (liver and skin) 3β-hydroxysteroid dehydrogenase type 1 converts DHEA to androstenedione which provides low levels of androgen activity. These levels are enough to cause clitoral enlargement, acne, and hirsutism in females but not enough to lead to proper male development. Hence, these patients present with:

- Cortisol deficiency
  - Adrenal insufficiency
- Mineralocorticoid deficiency
  - Hypotension
  - Hyperkalemia
- Androgen excess
  - Ambiguous genitalia in males
  - Mild to moderate clitoral enlargement, hirsutism, and acne in females

Generally, these patients present as neonates or early infants with feeding difficulties, vomiting, volume depletion, and other above features.

22. How do patients with nonclassical CAH present?

Patients with nonclassical CAH (also called late-onset CAH) produce normal amounts of cortisol and aldosterone with mild to moderate overproduction of sex hormone precursors. DHEAS levels are often elevated. The prevalence of nonclassical CAH in women presenting with hyperandrogenic signs and symptoms is approximately 2.2%. Thus, a follicular phase 17-OHP should be included in the evaluation of any female patient with hyperandrogenic symptoms. Usually, these patients are asymptomatic with normal external genitalia but may present with the following:

- Premature puberty
- Severe cystic acne – occurring in 33% of patients
- Hirsutism – most common symptom, occurring in 60% of symptomatic females
- Oligomenorrhea and polycystic ovaries – second most common, occurring in 54% of patients
- Infertility – occurring in 13% of patients

23. Summarize the relationship between adrenal "incidentalomas" and CAH.

Adrenal incidentalomas are more common in patients with CAH and in carriers. Additionally, 60% of patients with incidentalomas have exaggerated 17-OH progesterone responses to ACTH.

24. Summarize the relationship between Ehlers-Danlos syndrome and CAH.

The *CYP21A2* gene encoding for the 21-hydroxylase enzyme P450c21 is located on chromosome 6p21.33. Nearby is the *TNXB* gene that encodes the extracellular matrix glycoprotein tenascin-X (TNX), which promotes collagen deposition in the skin and connective tissue of the heart and skeletal muscle. *TNXB* deficiency is associated with Ehlers-Danlos syndrome (EDS). Chimeric recombination during meiosis can result in a contiguous *CYP21A2* and *TNXB* gene deletion, causing a condition known as CAH-X syndrome. This syndrome is underdiagnosed and may affect as many as 10% of patients with salt-wasting CAH. Cardiac ultrasound is helpful to detect cardiac valvular disorders in these patients.

25. Describe the clinical features that suggest the possibility of CAH.

Adrenal crisis or severe salt-wasting in the newborn period suggests the possibility of CAH. CAH should also be strongly considered in the differential diagnosis of any newborn with ambiguous genitalia. Because adrenal crisis and salt loss in CAH may be fatal if not treated, the finding of ambiguous genitalia in a newborn should trigger a rapid attempt to confirm or exclude CAH. Most males with CAH do not have ambiguous genitalia; consequently, many cases go unrecognized at birth unless there is a documented family history of the disorder.

26. What clinical clues help support or refute the diagnosis of CAH in a newborn with ambiguous genitalia?

The overwhelming majority of genetic males with CAH have unambiguous external genitalia at birth. If external genitalia is ambiguous, the finding of palpable gonads in the scrotal or inguinal area confirms the presence of testes and genetic male sex. Determination of male sex makes CAH unlikely, and decreases diagnostic urgency, as disorders giving rise to ambiguous genitalia in genetic males are rarely associated with a fatal outcome. Conversely, the detection of a uterus in an infant with ambiguous genitalia, either by physical examination or by ultrasound, strongly suggests that the infant is a genetic female, and heightens the possibility of CAH.

27. Discuss the role of molecular biology techniques in the diagnosis of CAH.

Molecular techniques can rapidly confirm the genetic sex of a newborn without the prolonged wait for a traditional chromosome analysis. Because of the potentially severe consequences of CAH, it is prudent to assume that any genetic female with ambiguous genitalia has CAH until proven otherwise. Furthermore, it is recommended to wait to assign gender until molecular testing is done, as gender misassignment may cause long-term psychological problems for the families of such children. Early diagnosis and appropriate therapy also allow one to avoid the progressive effects of excess adrenal androgens, which will cause short stature, gender confusion in girls, and psychosexual disturbances in both boys and girls.

28. How is the diagnosis of CAH confirmed?

Because one does not know which enzyme is deficient in a newborn with suspected CAH (unless the family has a documented history of a particular enzyme defect), serum levels of all steroids that may be in the affected biosynthetic pathway can be measured before and after the administration of 250 mcg of synthetic ACTH. Urinary measurement of these steroids by gas chromatography/mass spectroscopy has also recently become economically feasible. Plasma renin activity and aldosterone levels should also be measured to assess the adequacy of aldosterone synthesis. Determination of which steroid levels are supranormal and which are low facilitates localization of the exact enzyme block.

29. How are specific genetic defects confirmed?

Specific genetic defects may be confirmed with molecular genetic testing. Polymerase chain reaction (PCR) amplification for the rapid simultaneous detection of the 10 mutations that are found in approximately 95% of 21-hydroxylase deficiency alleles is used for rapid results. Molecular genetic analysis of CYP21 is not essential for diagnosis but may be helpful to:

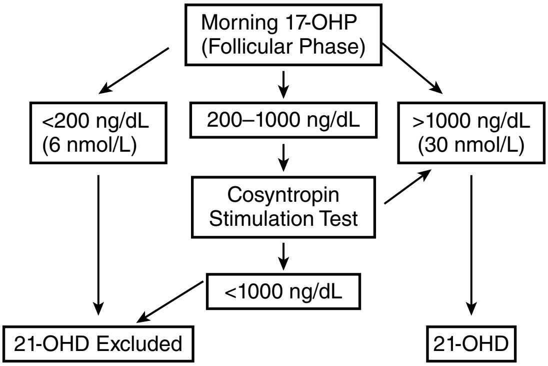

Fig. 38.3 Algorithm for diagnosing nonclassical CAH.

- confirm the basis of the defect
- aid in genetic counseling
- establish the disease in certain cases

30. What should be done when nonclassical CAH is suspected in older patients?

When nonclassical CAH is suspected in the preteen, teenage, or adult patient, obtain an early morning 17-OHP level. If levels are <200 ng/dL then CAH is excluded, while levels >1,000 ng/dL confirm CAH (Fig. 38.3). If levels are between 200–1000 ng/dL then proceed with ACTH stimulation testing. ACTH stimulation testing should be done with 250 mcg (not 1 mcg) of synthetic ACTH; measurement of 17-OHP, 17-OH pregnenolone, androstenedione, DHEA, and cortisol should be done before and 60 minutes after injection. Stimulated levels of 17-OHP with classical CAH are typically greater than 10,000 ng/dL, while patients with nonclassical CAH will usually have 17-OHP levels in the range of 1000–10,000 ng/dL. Hyperandrogenism can be assessed in women by measuring serum levels of testosterone, androstenedione, and 3-α-androstanediol glucuronide.

31. Describe the test used for newborn screening.

The screening process for newborns is divided into first-tier and second-tier screening tests. First-tier screening for CAH focuses on the rapid detection of classic 21-hydroxylase deficiency on Guthrie cards (filter paper on which blood samples are collected, dried, and transported) measured by automated time-resolved dissociation-enhanced lanthanide fluoroimmunoassay. This screening method measures 17-OHP. Basal 17-OHP usually exceeds 10,000 ng/dL in affected infants, whereas the level in normal infants is below 100 ng/dL. To have a high level of sensitivity, cutoff values are set to low in order to have 1% of all tests reported as positive thus leading to several false positive results. Infants that are premature, sick, or stressed will have higher levels of 17-OHP. Second-tier testing includes molecular genetic testing or biochemical testing that measures steroid ratios by liquid chromatography followed by mass spectrometry. As of 2009, all 50 states in the United States and at least 12 other countries screened for CAH. Fig. 38.4 outlines the algorithm normally used.

32. What other tests may be used?

If CAH is suspected and newborn filter paper screening is not available, ACTH stimulation with steroid precursor measurements should be performed after the first 24 hours of life. Adrenal ultrasound can also be used as a potential screening test for CAH neonates with ambiguous genitalia and/or salt-losing crisis by detecting >4 mm adrenal limb width.

33. How is CAH treated in neonates?

The most important goal of treatment is to prevent salt loss and adrenal crisis in the newborn period. This requires prompt administration of glucocorticoids and, in many cases, mineralocorticoids, as well as careful monitoring of salt intake. This treatment not only replaces the deficient

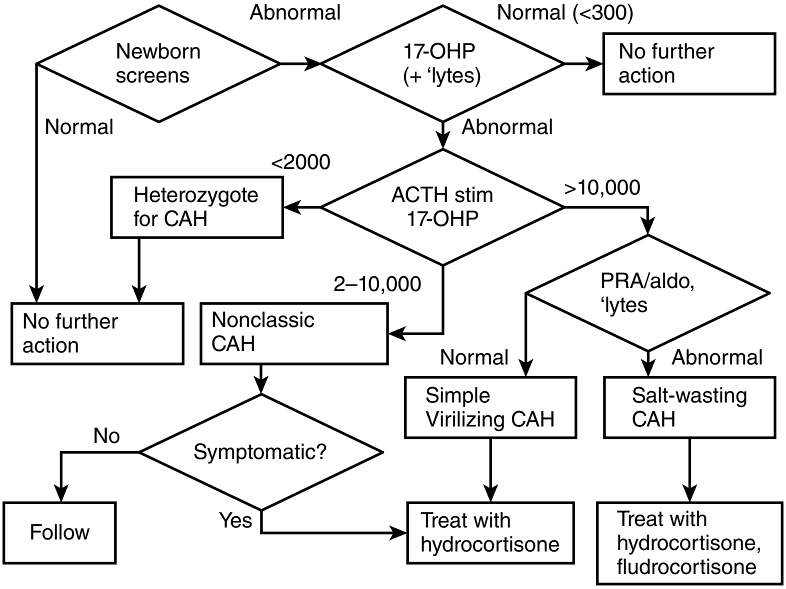
Newborn screens
Abnormal
17-OHP (+ 'lytes)
Normal (<300)
No further action
Normal
Abnormal
<2000
Heterozygote for CAH
ACTH stim 17-OHP
>10,000
2–10,000
PRA/aldo, 'lytes
No further action
Nonclassic CAH
Normal
Abnormal
Simple Virilizing CAH
Salt-wasting CAH
No
Symptomatic?
Follow
Yes
Treat with hydrocortisone
Treat with hydrocortisone, fludrocortisone

Fig. 38.4 Algorithm for screening for CAH in neonates.

hormones but also suppresses elevated serum ACTH levels, reducing adrenal production of androgenic precursors and metabolites. Such treatment may be given presumptively while awaiting results of definitive laboratory tests and then discontinued if the tests are not confirmatory.

34. What is the appropriate hydrocortisone formulation in infants and children unable to take a tablet?

The hydrocortisone tablet and suspension are not bioequivalent, and the suspension may have uneven distribution. Infants and children unable to take a tablet should take crushed hydrocortisone tablets in liquid.

35. When is the surgical correction of ambiguous genitalia carried out?

Surgical correction of ambiguous genitalia in girls consists of genitoplasty of the clitoris and labia and vaginoplasty. Single-stage surgery is now implemented between 2 and 6 months of life. Variable degrees of impairment of psychosexual functioning may occur in adulthood depending on the method, timing, and underlying mutation. Evidence has shown that patients with more severe mutations have lower sexual function scores, lower satisfaction with their sexual life, and more surgical complications.

36. Describe the treatment of CAH in children.

The preferred glucocorticoid for chronic replacement is hydrocortisone in doses of 10–15 mg/m^2/day in three divided doses. Hydrocortisone is preferred because of its short half-life, which minimizes growth suppression and other Cushing-like side effects. It is sometimes extremely difficult or impossible to find a dosage of glucocorticoid that normalizes the production of androgens and maintains normal growth and weight gain. In such situations, mineralocorticoids (fludrocortisone) and/or spironolactone/flutamide (androgen receptor blockers that prevent virilization) in combination with the aromatase inhibitor testolactone (which prevents estrogen-induced epiphyseal fusion) may be useful adjunctive therapy in combination with nonsuppressive replacement doses of glucocorticoids. Multiple glucocorticoid-sparing agents are also under investigation as an option to preserve height in pediatric patients. Rarely, adrenalectomy has been used for difficult-to-control patients since treatment of adrenal insufficiency is relatively much simpler. All patients with salt-wasting CAH should be treated with fludrocortisone with recommended dosing of 0.05–0.2 mg/day given once or twice a day.

Crinecerfont, a corticotropin-releasing factor Type 1 antagonist, is newly FDA approved for treatment of classical CAH in adults and children age 4 years and older. Crinecerfont reduces ACTH and adrenal androgen production, and may allow for use of a lower glucocorticoid dose that reduces the risks of steroid overexposure. Weight-based dosing for children is between 25 and 100 mg twice daily. Concomitant use of a glucocortoid agent is still required to prevent adrenal insufficiency.

37. How is CAH treated in adolescents and adults?

The use of growth hormone, a gonadotropin-releasing hormone analog (GNRHa), antiandrogens, and aromatase inhibitors alone or in various combinations may improve final predicted height, particularly in those whose predicted height is ≤2.25 S.D.'s. Such treatments should be done within an Institutional Review Board (IRB)-approved protocol because both the necessity and the long-term consequences of such an approach have yet to be determined. Prednisone (5–7.5 mg daily in two divided doses) or dexamethasone (0.25–0.5 mg daily) may be used once growth has been completed. Because of the potency of dexamethasone, intermediate doses can be achieved by using liquid dexamethasone (1 mg/ml), which is generally used for other conditions in infants and children. Liquid prednisolone is another reasonable option that allows for flexible dose titration. Patients should be monitored carefully for signs of iatrogenic Cushing's syndrome and sonography used in males to detect testicular adrenal rest tumors. Adrenalectomy is *NOT* a recommended approach, as these patients are more likely to experience adrenal crisis.

Crinecerfont is a newly FDA-approved agent for treatment of classical CAH. As a corticotropin-releasing factor Type 1 antagonist, crinecerfont inhibits pituitary ACTH levels and reduces adrenal androgen production, allowing for reduced corticosteroid dosing. Adult crinecerfont dosing is 100 mg twice daily. The patient's preexisiting glucocorticoid regimen should be continued at onset of therapy, and the steroid can be gradually tapered to target normal androstenedione levels. The patient must continue enough glucocorticoid to avoid adrenal insufficiency. Studies are ongoing to examine the safety of crinercerfont use during pregnancy.

38. What is the role of glucocorticoid treatment in nonclassical CAH?

Glucocorticoid therapy is not recommended in asymptomatic patients, as they are unlikely to suffer from adrenal insufficiency. Considerations for initiation of glucocorticoid therapy in nonclassical CAH patients include:

- Evidence has shown that women with nonclassical CAH on glucocorticoid therapy have a lower miscarriage rate compared to women not on glucocorticoids.
- If the patient has inappropriately early onset and rapid progression of pubarche/bone age or over-virilization, glucocorticoids can be initiated and then discontinued after the adult height is attained.
- If the patient has significant hyperandrogenism, therapy can be considered.
- Glucocorticoid therapy may benefit women with infertility or those with a history of miscarriage.
- Testicular adrenal rest tumors are rare in male patients with nonclassical CAH, thus glucocorticoid therapy is not indicated.

39. Are any new therapies for CAH treatment under development?

Modified-release hydrocortisone is being tested as a treatment option to better mimic the diurnal variation of cortisol and offer better biochemical control compared to standard glucocorticoid therapy. Abiraterone, a potent 17A1 inhibitor, is showing promise to normalize androgens in CAH patients. Tildacerfont, a CRF1 receptor antagonist with a mechanism similar to crinecerfont, did not demonstrate reduction of ACTH levels during phase 2 trials and has been discontinued.

40. Are any new laboratory tests being developed to detect and monitor CAH?

Assays of androgen intermediates such as the 11-oxygenated C19 steroids (11-ketotestosterone, 11-hydroxytestosterone, 11-hydroxyandrostenedione, 11-ketoandrostenedione) are not commercially available but, in translational studies, elevations of these compounds correlate with adrenal androgen production in CAH.

TABLE 38.1 Recommended Initial Treatment for Patients With CAH Exposed to Clinically Significant Medical Stress

PATIENT'S AGE	INITIAL PARENTERAL HYDROCORTISONE DOSE
Infants and preschool children	25 mg
School-age children	50 mg
Adults	100 mg

CAH, Congenital adrenal hyperplasia.

41. What factors favor the achievement of predicted adult height?

- Early CAH diagnosis.
- Lower doses of hydrocortisone in the first year of life.
- Use of hydrocortisone rather than prednisone or dexamethasone during the pubertal growth spurt.
- Mineralocorticoid treatment in all patients who are genetically determined to be salt-wasters even if they are not so clinically.

42. What changes in therapy are necessary as a result of medically significant stress?

Patients with CAH who have been on steroid therapy should wear a medical alert bracelet or necklace and should be provided with an emergency kit of hydrocortisone or dexamethasone for intramuscular use. For medically significant stress, the following measures are recommended (Table 38.1):

- Triple the oral dose of glucocorticoids.
- Use intramuscular (or intravenous) steroids if the patient is unable to consume oral medications. Hydrocortisone is the preferred glucocorticoid because of its mineralocorticoid properties.
- Sodium chloride, 1–2 g/day, may be necessary in infants.
- Higher doses of fludrocortisone acetate (Florinef) are not recommended during severe stress. The mineralocorticoid effects of hydrocortisone are sufficient.
- Successive IV hydrocortisone doses should be given as three to four times maintenance doses per day, divided every 6 hours.

43. What changes in therapy are necessary during pregnancy for patients with classical CAH?

- Continue the previous dose of glucocorticoids in the first and second trimesters, but may adjust the dose if symptoms of glucocorticoid insufficiency occur.
- Use glucocorticoids that do not traverse the placenta (placental 11B-HSD2 is responsible for the degradation of certain glucocorticoids) such as hydrocortisone or prednisone rather than dexamethasone. Dexamethasone passes through the placenta unmetabolized.
- Increase the glucocorticoid dose during the third trimester by 20–40%.
- Use stress doses of steroids during labor and delivery.

44. What changes in therapy are necessary during pregnancy for patients with nonclassical CAH?

Current recommendations are to consider treatment with glucocorticoids if patients have had a previous miscarriage. Hydrocortisone is the preferred glucocorticoid, as it is metabolized by the placenta and will not affect the fetus. Dexamethasone is *NOT* recommended, as it is able to cross the placenta. Stress dosing is usually not necessary unless patients have a documented prior suboptimal response to the ACTH stimulation test (<14–18 ug/dL).

45. How is treatment monitored?

The goals of treatment are to prevent symptoms of adrenal insufficiency and to suppress ACTH and adrenal androgen production. For the latter, it is most appropriate to monitor the levels of the key precursors immediately behind the blocked enzyme (e.g., 17-OHP and androstenedione in the case of 21-hydroxylase deficiency). The goal is not to normalize the 17-OHP level since this will lead to iatrogenic Cushing's syndrome. Monitoring should be performed every 3 months initially and then every 4–12 months. The goal is to normalize serum sodium, potassium, testosterone, and androstenedione levels. In women attempting pregnancy, the follicular phase progesterone level should be <0.6 ng/mL.

46. What other monitoring tools may be beneficial?

Androgen levels should be monitored during treatment. These include testosterone, androstenedione, and 3-α-androstanediol glucuronide. Plasma renin activity should be monitored in patients with salt-wasting CAH. Children must have annual bone age determinations, and their height should be carefully monitored. Because patients with CAH carry increased risks for cardiovascular disease, they should be routinely monitored and treated for cardiovascular disease which may begin at an earlier age than normal. Adult men with CAH are prone to develop testicular adrenal rest tumors and may have reduced fertility. This can be monitored by serial ultrasound and semen analysis, if appropriate.

47. What genetic preconception counseling is appropriate for patients with nonclassical CAH?

Patients and partners should both be screened for 21-hydroxylase deficiency, as patients with nonclassical CAH have a 30–50% chance of carrying one allele encoding for a severe defect in enzyme function. If a child inherits this allele from both parents, classical CAH will result.

48. What genetic preconception counseling is appropriate for a couple who previously had a child with CAH?

Because all forms of CAH are autosomal recessive disorders, both parents of a child with CAH are obligate heterozygote carriers of the gene defect. Consequently, the chance that another child of the same couple will have CAH is one in four; 50% of the children will be heterozygote carriers. Genetic counseling should be offered to all parents who have a child with CAH. Modern genetic techniques and chorionic villus sampling of fetal DNA at 9 weeks of gestation allow the diagnosis of CAH during the first trimester of pregnancy. The other use for genotypic identification includes the prediction of the phenotype (i.e., severity of the disease). There appears to be a good relationship between genotype and phenotype in classic but not in nonclassic CAH.

49. Are any prenatal treatments available for the fetus with CAH?

Glucocorticoid treatment of the fetus with 21-hydroxylase deficiency should be regarded as experimental at this time and only be done in the context of an IRB-approved protocol. Earlier recommendations for such treatment were based on small and uncontrolled studies. The potential adverse effects of glucocorticoid therapy in this setting may outweigh any benefits.

KEY POINTS

CAH

- CAH is a group of autosomal recessive disorders that impact adrenal steroid synthesis, the most frequent of which is 21-hydroxylase deficiency.
- The most serious consequences of CAH are ambiguous genitalia in females at birth, neonatal salt-wasting, short stature, and premature puberty.
- CAH is diagnosed through measurement of cortisol precursors before and 1 hour after the intravenous administration of 250 μg of synthetic ACTH.
- Predicted adult height can be achieved through early diagnosis, lower doses of corticosteroids in the first year of life and during puberty, and the use of fludrocortisone even in those who are salt-wasters genetically but not clinically.
- CAH is a rare cause of ambiguous genitalia in a genetic male.
- The most common symptom of nonclassic CAH in females is hirsutism.
- Prenatal treatment with dexamethasone and height-enhancing treatment with growth hormone and/or GNRHa should be done only under IRB-approved protocols in centers of excellence.

WEBSITES

http://www.endocrine.org
https://academic.oup.com/jcem/article/103/11/4043/5107759

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CHAPTER 39

Thyroid Testing

Michael T. McDermott

1. What is the single best test to screen for abnormal thyroid gland function?

Serum thyroid-stimulating hormone (TSH) is the best initial test for assessing thyroid function because most thyroid dysfunction is due to primary thyroid disease, to which the pituitary gland responds with predictable changes in TSH secretion. Situations in which serum TSH levels do not accurately reflect thyroid function include pituitary-hypothalamic disorders, nonthyroidal illnesses, and the use of certain medications such as glucocorticoids, dopamine, and somatostatin analogs. Measurement of serum thyroxine (T4) and triiodothyronine (T3) is useful when TSH levels are outside the reference range (Fig. 39.1).

2. How do you interpret the serum TSH level?

TSH is the primary regulator of thyroid function. The hypothalamic-pituitary unit exerts exquisite control over the thyroid system, resulting in a log-linear relationship between serum TSH and thyroid hormone (T4 + T3) levels. Accordingly, small changes in T4 or T3 production result in large changes in TSH levels. Abnormal serum TSH values appear long before serum T4 and T3 levels are outside their reference ranges. If the TSH is elevated, the patient usually has primary hypothyroidism; a serum-free T4 level should then be ordered. When TSH is low, primary hyperthyroidism is the usual cause; serum-free T4 and total or free T3 should then be ordered. It should also be kept in mind that TSH secretion has a diurnal pattern with the highest serum TSH levels occurring in the late afternoon and evening.

3. Explain how the serum TSH is used to manage patients on thyroid hormone therapy.

Thyroid hormone therapy is usually given for one of two purposes: replacement therapy for hypothyroidism or suppression therapy for thyroid cancer. When replacement is the goal, the dosage should be adjusted to maintain serum TSH within the reference range. When suppression is the goal, the dosage should be adjusted to maintain serum TSH in the low normal, slightly low, or undetectable range depending on individual circumstances and goals.

4. What do total T4 and T3 assays measure?

Approximately 99.98% of circulating T4 and 99.70% of T3 are bound to proteins, such as thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA or transthyretin), and albumin (Fig. 39.2). Total T4 and T3 assays measure the total amounts of T4 and T3

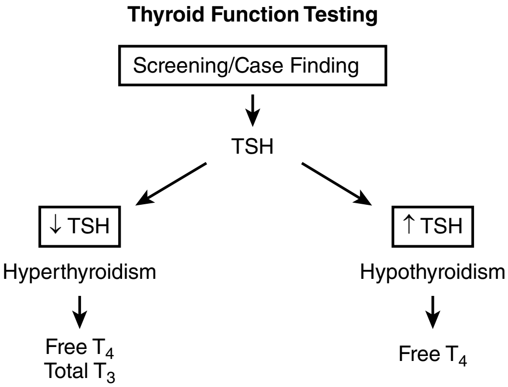

Fig. 39.1 Thyroid Hormone Testing Strategy.

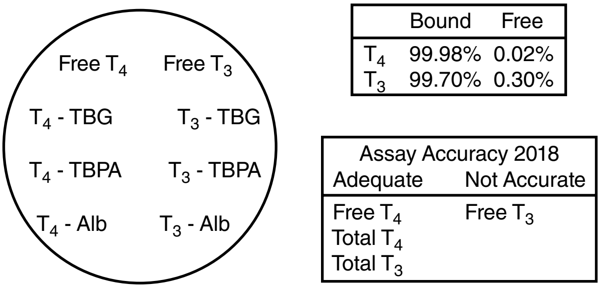

Fig. 39.2 Protein-bound and Free Thyroid Hormones in the Circulation.

(protein-bound and free) in the circulation. Serum total T4 and T3 levels can be altered significantly by protein binding disorders.

5. Discuss the advantages of free thyroid hormone assays.

Free T4 and T3 assays measure the unbound, bioactive thyroid hormones in the circulation. Free thyroid hormone tests fall into two main categories: equilibrium dialysis and analog assays. Equilibrium dialysis methods are more accurate because they are not affected by thyroid hormone–binding protein abnormalities, but they are expensive. Analog methods, which are used by most commercial laboratories, are variably affected by protein binding. It is important for practitioners to establish the accuracy of the free T4, and T3 assays they use.

6. What is reverse T3 and when should it be measured?

T4 is the primary hormone secreted by the thyroid gland. Circulating T4 is converted into T3 in the liver and kidneys by deiodinase 1 (D1) and in the brain by deiodinase 2 (D2). T4 can also be converted into Reverse T3 (RT3) by deiodinase 3 (D3) (see Chapter 46).

RT3 is considered an inactive thyroid metabolite; RT3 has a 100-fold lower affinity than T3 for the T3 receptor. During nonthyroidal illness, serum T3 decreases and RT3 rises due to decreased activity of D1. Conversely, D1 activity is enhanced in hypothyroidism, promoting more conversion of T4 to T3 and less conversion to RT3. As a result, RT3 is usually low in hypothyroidism. RT3 measurement is not indicated for the evaluation of most thyroid conditions but can be helpful in distinguishing central hypothyroidism from nonthyroidal illnesses (euthyroid sick syndrome). Serum TSH, T4, and T3 can be low in both conditions, but RT3 is usually low in central hypothyroidism and high in euthyroid sick syndrome.

7. Name the major disorders of thyroid hormone–binding proteins.

Pregnancy, estrogen use, congenital TBG excess, and familial dysalbuminemic hyperthyroxinemia (FDH) are the most common. FDH is an inherited disorder in which albumin has enhanced affinity for T4, resulting in increased levels of total T4 but not T3. Protein binding of T4 and T3 is reduced by androgens and congenital TBG deficiency.

A T3 resin uptake (T3RU) measurement helps distinguish protein binding disorders from true thyroid diseases. The T3RU is inversely proportional to protein-binding capacity; accordingly, T3RU is low when T4 protein binding is increased and high when protein binding is reduced. Table 39.1 indicates how these tests are used to make the correct diagnosis.

TABLE 39.1 Diagnosing Disorders of Thyroid Hormone–Binding Proteins

	TOTAL T4	TOTAL T3	T3RU
Hyperthyroidism	↑	↑	↑
Increased protein-binding state	↑	↑	↓
Hypothyroidism	↓	↓	↓
Decreased protein-binding state	↓	↓	↑

T4, thyroxine; *T3*, triiodothyronine; *T3RU*, triiodothyronine resin uptake.

8. What antithyroid antibody tests are clinically useful?

Antithyroperoxidase (TPO) and antithyroglobulin antibodies are markers of Hashimoto's thyroiditis; TPO antibodies are the more sensitive test. TSH receptor antibodies (TRAb) and thyroid-stimulating immunoglobulins (TSI) are markers of Graves' disease. Positive levels establish the diagnosis and their subsequent disappearance heralds remission.

9. How useful are thyroglobulin measurements?

Thyroglobulin (TG) is the major iodoprotein constituent of thyroid follicles. Serum TG levels are mildly increased in many thyroid diseases, but marked elevations are seen mainly with active thyroid cancer and in destructive thyroiditis (subacute, postpartum, or silent thyroiditis). TG measurements are useful for monitoring patients with thyroid cancer. Low or undetectable levels indicate a good response to therapy while rising or elevated levels suggest the presence of residual or metastatic thyroid cancer. Most TG assays are not reliable in the presence of anti-TG antibodies, which interfere with the method of TG measurement.

10. When should a serum calcitonin level be measured?

Calcitonin is made by thyroid parafollicular C cells and not by follicular cells. Serum calcitonin is elevated in medullary carcinoma of the thyroid (MCT) and its precursor lesion, C-cell hyperplasia. Because MCT is an uncommon thyroid neoplasm, serum calcitonin measurements are not recommended in the routine evaluation of most thyroid nodules. However, calcitonin measurement is indicated if a patient has a family history of MCT, MEN2A, or MEN2B or has associated diarrhea, which is characteristic of MCT.

11. Discuss the interpretation of the radioactive iodine uptake (RALU) test.

Thyroid follicular cells have sodium iodine symporters (NIS) that transport iodine into the cells for thyroid hormone synthesis. Symporter activity can be assessed with a radioactive iodine uptake (RAIU). A normal 24-hour RAIU is 10–30% in the United States, but it varies according to location because of geographic differences in dietary iodine intake. RAIU is most useful in the differential diagnosis of thyrotoxicosis by distinguishing two distinct categories: high-RAIU thyrotoxicosis and low-RAIU thyrotoxicosis (see Table 39.2).

12. When and why should a thyroid scan be ordered?

A thyroid scan helps to distinguish the three most common types of high-RAIU thyrotoxicosis. Graves' disease shows diffuse tracer uptake; toxic multinodular goiter shows patchy areas of increased uptake; the solitary toxic adenoma shows a single area of intense uptake. The scan is not helpful in low-RAIU thyrotoxicosis. A thyroid scan is not recommended in the evaluation of thyroid nodules unless the serum TSH is low, in which case the scan can detect the presence of functioning (hot) nodules.

13. How does high-dose biotin interfere with thyroid tests?

Biotin is a reagent component for immunoassays of many hormones. People who take high doses of biotin supplements (5,000–20,000 mcg/day for hair loss and brittle nails) can have falsely abnormal, hormone measurements during biotin ingestion. High biotin concentrations can

TABLE 39.2 High-RAIU Thyrotoxicosis and Low-RAIU Thyrotoxicosis Categories

HIGH-RAIU THYROTOXICOSIS	LOW-RAIU THYROTOXICOSIS
Graves' disease	Factitious thyrotoxicosis
Toxic multinodular goiter	Iodine-induced thyrotoxicosis
Solitary toxic adenoma	Subacute thyroiditis
TSH-secreting tumor	Postpartum thyroiditis
Human chorionic gonadotropin (HCG)-induced thyrotoxicosis	Silent thyroiditis

RAIU, radioactive iodine uptake; *TSH*, thyroid-stimulating hormone.

falsely elevate levels (free T4, free T3, TRAb, cortisol, testosterone, estradiol) in biotin-streptavidin competitive immunoassays and falsely lower levels (TSH, PTH, ACTH, LH, FSH) in biotin-streptavidin immunometric assays. Graves' disease can thus be erroneously diagnosed (low TSH, high free T4 and T3, positive TRAb) in someone taking high-dose biotin. An 8-hour abstinence from biotin often corrects this anomaly, but most authorities recommend ≥3 days of abstinence.

14. What are heterophile antimouse antibodies?

Heterophile antimouse antibodies (HAMA) sometimes develop in people who are regularly exposed to rodents, such as laboratory workers, farm workers, and other people who spend a lot of time outdoors, including homeless people. HAMA can interfere with the measurement of several hormones, including TSH and thyroglobulin. When TSH or thyroglobulin values are not consistent with the clinical picture, interference by HAMA should be suspected and the patient questioned about possible sources of exposure. Measuring serum HAMA can identify these antibodies or notifying the lab that HAMA is a possibility will allow the lab to test the serum by a method that avoids interference by HAMA.

15. What is MACRO-TSH?

Macro-TSH refers to large molecular complexes of TSH bound to anti-TSH autoantibodies, most commonly in the context of autoimmune disease. These complexes interfere with accurate TSH measurement, resulting in anomalous TSH elevations in the presence of normal free T4 levels. While elevated serum TSH in the presence of normal free T4 levels usually indicates subclinical hypothyroidism, the presence of macro-TSH may be considered when elevated TSH levels are otherwise not consistent with the clinical presentation. Macro-TSH can be detected by gel filtration chromatography or polyethylene glycol (PEG) precipitation.

KEY POINTS

Thyroid Testing

- TSH is the best test to screen and evaluate people for thyroid disease and to monitor thyroid hormone replacement therapy.
- Free thyroxine (T4) should be measured when TSH is elevated, and free T4 and free or total triiodothyronine (T3) should be measured when TSH is suppressed.
- TPO antibodies are the most accurate test to establish a diagnosis of chronic lymphocytic thyroiditis (Hashimoto's disease).
- Serum thyroglobulin (TG) is useful for monitoring for recurrence of differentiated thyroid cancer and for assisting in the diagnosis of destructive thyroiditis.
- The RAIU is used primarily to determine whether patients with thyrotoxicosis have a high RAIU or a low RAIU disorder.
- A thyroid scan is used mainly to distinguish among the three most common types of high-RAIU thyrotoxicosis: Graves' disease, toxic multinodular goiter, and toxic adenoma.
- Biotin supplements, HAMA, and macro-TSH can cause significant interference with assays used to evaluate thyroid function.

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Hyperthyroidism

Thanh Duc Hoang and Henry B. Burch

1. What is the difference between thyrotoxicosis and hyperthyroidism?

Thyrotoxicosis is the general term for the presence of increased levels of thyroxine (T4), triiodothyronine (T3), or both, from any cause. It does not imply that a patient is markedly symptomatic or "toxic." Hyperthyroidism refers to causes of thyrotoxicosis in which the thyroid is actively overproducing thyroid hormone.

2. Define the term “autonomy” as it applies to thyroid hyperfunction.

Thyroid autonomy refers to the spontaneous production and secretion of thyroid hormone, independent of thyroid-stimulating hormone (TSH).

3. What is subclinical thyrotoxicosis?

Subclinical thyrotoxicosis is a biochemically defined disease with a low serum TSH level with free T4 and T3 levels that are still within the reference range. The low TSH concentration can result from either ingestion of excessive thyroid hormone or excessive release of endogenous thyroid hormone. Free T4 or T3 levels are frequently in the high normal range in affected patients. Clinical symptoms and signs are generally absent or nonspecific.

4. What are the long-term consequences of subclinical thyrotoxicosis?

Some studies have linked subclinical thyrotoxicosis to (1) progression to clinical thyrotoxicosis; (2) skeletal effects, including decreased bone mineral density, accelerated bone loss, and increased fracture risk, particularly in postmenopausal women; (3) cardiac effects, such as a two- to three fold higher risk of atrial fibrillation, tachycardia, atrial premature beats, impaired left ventricular diastolic filling and impaired ventricular ejection fraction response to exercise; and (4) dementia and cognitive dysfunction. A recent extensive metaanalysis by Collet and colleagues found an increased rate of both cardiovascular and all-cause mortality in patients with subclinical hyperthyroidism. A TSH value below 0.1 mU/L is more likely to be associated with adverse consequences than a TSH value in the 0.1–0.5 mU/L range.

5. What are the long-term consequences of subclinical thyrotoxicosis?

The 2016 American Thyroid Association (ATA) Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis suggest that patients with TSH <0.1 mU/L who are older than age 65 or who are younger but with symptomatic disease or comorbidities that may be aggravated by mild hyperthyroidism (i.e., coronary heart disease, osteoporosis, postmenopausal symptoms, hyperthyroid symptoms) should be actively treated. Patients with TSH values between 0.1 and 0.4 mU/L should at least be *considered* for therapy if greater than age 65 or younger but with comorbidities as above.

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6. List the three most common causes of hyperthyroidism.

- Graves' disease (autoimmune hyperthyroidism)
- Toxic multinodular goiter (TMNG)
- Toxic adenomas or autonomously functioning thyroid nodules (AFTNs)

7. Define Graves’ disease.

Graves’ disease is an autoimmune disease in which autoantibodies directed against the TSH receptor result in continuous stimulation of thyroid hormone production and secretion as well as thyroid growth (goiter). Extrathyroidal manifestations of Graves' disease include orbitopathy (manifest as proptosis, periorbital edema, extraocular muscle dysfunction, and optic neuropathy), dermopathy (pretibial myxedema), and thyroid acropachy (digital clubbing and edema).

8. Explain TMNG.

TMNG generally arises in the setting of a long-standing multinodular goiter in which certain individual nodules have developed autonomous function and secrete thyroid hormone independent of stimulation by TSH.

9. What are AFTNs?

Autonomously functioning thyroid nodules (AFTNs) or toxic adenomas are benign tumors that have constitutive activation of the TSH receptor or its signal-transduction apparatus. These tumors frequently produce subclinical thyrotoxicosis and may have a predilection for spontaneous intranodular hemorrhage or degeneration. AFTNs generally must be larger than 3 cm in diameter before attaining sufficient secretory capacity to produce overt thyrotoxicosis. Often, inefficient iodine processing leads to an excess of T3 relative to T4 in AFTNs.

10. What is the Jod-Basedow phenomenon?

The Jod-Basedow phenomenon is named after the German physician, Dr. Karl Adolph Von Basedow, who first described the phenomenon, and the German word for iodine, “Jod.” The term refers to thyrotoxicosis that can occur after exposure to large quantities of iodine (typically in iodinated radiographic contrast agents for CT imaging or angiography, but also with the antiarrhythmic drug, amiodarone). Historically, it was first described following iodine supplementation in people living in regions of endemic iodine deficiency, which is associated with the development of autonomous thyroid nodules.

11. What are some rare causes of thyrotoxicosis?

Rare causes of thyrotoxicosis include TSH-secreting pituitary adenomas; stimulation of TSH receptors by high levels of human chorionic gonadotropin (hCG), most often in choriocarcinomas in women (gestational trophoblastic disease) or germ cell tumors in men; struma ovarii (ectopic thyroid hormone production in thyroid tissue–containing ovarian teratomas); and functional metastatic follicular or papillary thyroid carcinoma. Thyroiditis (postpartum, subacute, painless, drug-induced, i.e., amiodarone, checkpoint inhibitor, alemtuzumab), radiation, palpation, and ingestion of excessive exogenous thyroid hormone (iatrogenic, inadvertent, or surreptitious) are causes of thyrotoxicosis but not hyperthyroidism (see Question 1).

12. How do thyrotoxic patients present clinically?

Common symptoms include palpitations, anxiety, agitation, tremor, restlessness, insomnia, impaired concentration/memory, irritability or emotional lability, weight loss, heat intolerance, sweating, exertional dyspnea, fatigue, hyperdefecation, amenorrhea, oligomenorrhea, hypomenorrhea, anovulation, and hair thinning. Occasionally patients may experience weight gain rather than loss during thyrotoxicosis, presumably owing to polyphagia.

13. What is apathetic hyperthyroidism?

Older patients with hyperthyroidism may lack typical symptoms and signs of sympathetic activation and present instead with apathy or depression, weight loss, lethargy, atrial fibrillation, shortness of breath, worsening angina pectoris, or congestive heart failure.

14. Describe the physical signs of thyrotoxicosis.

Tremors, tachycardia, flow murmurs, systolic hypertension, warm and moist skin, thin and fine hair, hyperreflexia with rapid relaxation phases, lid lag/lid retraction (stare), proptosis, and goiter may be found in thyrotoxic patients. Some patients with Graves' disease also present with orbitopathy, pretibial myxedema, acropachy, and a thyroid bruit. Eye findings in thyrotoxicosis are discussed in Question 15.

15. What causes thyroid eye disease?

Lid retraction and stare can be seen with any cause of thyrotoxicosis and are due to sympathetic/adrenergic overactivity. True thyroid eye disease (TED) is unique to Graves' disease and is thought to be caused by thyroid autoantibodies that cross-react with antigens in fibroblasts, preadipocytes, and adipocytes of the retroorbital tissues. TSH receptor antibodies, activated T cells, and macrophages play an essential role in the pathogenesis of TED by activating orbital fibroblast and adipocyte TSHRs and IGF-1 receptors, leading to cellular expansion and orbital inflammation. Common manifestations of orbitopathy include proptosis, diplopia, eye irritation, excessive tearing, eye or retroorbital discomfort, blurred vision, color vision desaturation, vision loss or dysthyroid optic neuropathy in severe cases, and inflammatory changes such as conjunctival injection and periorbital edema.

16. What laboratory testing should be performed to confirm thyrotoxicosis?

Measurement of serum TSH with a third-generation assay (with detection limits of 0.01 mU/L) is the most sensitive means for detecting thyrotoxicosis. Serum-free T4 and T3 levels should be measured to determine the degree of biochemical thyrotoxicosis. Other associated laboratory findings may include mild leukopenia, normochromic normocytic anemia, hepatic transaminitis, elevated serum alkaline phosphatase and osteocalcin (increased bone turnover), mild hypercalcemia, hyperphosphatemia, low serum levels of albumin, and low levels of total, LDL, and HDL cholesterol.

17. When is thyroid antibody testing needed in patients with thyrotoxicosis?

The cause of thyrotoxicosis usually can be determined with history, physical examination, and radionuclide studies. Testing for TSH receptor antibodies can be used to diagnose Graves' disease during pregnancy when radionuclide imaging is contraindicated. It is also useful in (1) pregnant women with current or previously treated Graves' disease to determine the risk of fetal and neonatal thyroid dysfunction due to transplacental passage of stimulating or blocking antibodies; (2) biochemically euthyroid patients with orbitopathy; (3) patients with alternating periods of hyper and hypothyroidism as a result of fluctuations in blocking and stimulating TSH receptor antibodies; and (4) atypical cases when differentiation of Graves' disease from toxic multinodular goiter is challenging and therapeutically essential. The 2016 ATA Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis suggest that TSH-receptor antibody testing may be used as a diagnostic alternative to radioiodine uptake measurement to make the diagnosis of Graves' disease in a thyrotoxic patient.

18. What is the difference between a thyroid scan and an uptake?

A radioactive iodine uptake (RAIU) uses ^{131}I or ^{123}I to assess quantitatively the functional status of the thyroid gland. A small dose of radioisotope is given orally followed by measurement of radioactivity over the thyroid in 4–24 hours. Often two measurements are taken, at 4–6 hours and at 24 hours. A high uptake confirms hyperthyroidism whereas a low (nearly absent) radioiodine uptake indicates either destruction of thyroid tissue with the release of preformed hormone into the circulation or an extrathyroidal source of iodine or thyroid hormone. A thyroid scan provides a two-dimensional image showing the distribution of isotope trapping within the thyroid gland. Uniform distribution in a hyperthyroid patient suggests Graves' disease, patchy distribution suggests TMNG, and unifocal activity corresponding to a nodule, with suppression of the rest of the thyroid, suggests a toxic adenoma.

Table 40.1 provides a summary of expected testing results in common disorders of thyrotoxicosis.

19. Can a thyroid ultrasound be used to determine the etiology of thyrotoxicosis?

Assessment of thyroid blood flow by Doppler ultrasound can distinguish between the increased flow seen with active Graves' disease, sometimes referred to as "thyroid inferno," and the normal vascular flow pattern seen in patients with thyrotoxicosis due to destructive thyroiditis.

TABLE 40.1 Characteristics of Various Conditions Associated With Thyrotoxicosis

CONDITION	RAIU	TSH-RECEPTOR ANTIBODIES	DOPPLER-FLOW
Graves' disease	High	Positive	Increased
Toxic multinodular goiter	High-normal/high	Negative	Focally increased
Toxic solitary adenoma	High-normal/high	Negative	Focally increased
TSH-producing pituitary adenoma	High	Negative	Increased
HCG-producing choriocarcinoma	High	Negative	Increased
Subacute thyroiditis	Low	Negative	Decreased
Painless thyroiditis	Low	Negative	Decreased
Postpartum thyroiditis	Low	Negative	Decreased
Surreptitious thyroid hormone ingestion	Low	Negative	Decreased
Iodine-induced thyrotoxicosis	Low	Negative	Decreased
Struma ovarii	Low	Negative	Decreased

20. How should hyperthyroidism be treated?

The three main treatment options are antithyroid drugs (ATDs), radioiodine (^{131}I) ablation, and surgery. ATDs available in the United States include methimazole (MMI) and propylthiouracil (PTU). MMI is almost always the preferred agent. Due to concerns about severe hepatotoxicity, PTU is recommended only in (1) the first trimester of pregnancy (MMI has been linked to embryopathy when used during the first trimester); (2) thyroid storm therapy, because of the ability of PTU to block T4-to-T3 conversion; and (3) patients with minor reactions to MMI who refuse ^{131}I therapy or surgery. Unless contraindicated, most patients should receive beta-blockers for heart rate control and symptomatic relief. Although most patients in the United States have historically been treated with radioactive iodine rather than long-term ATDs or surgery, a growing majority of patients and providers are currently choosing long-term antithyroid drug therapy. Patients scheduled to receive ^{131}I should be advised to avoid pregnancy for 4–6 months and should be cautioned that oral contraceptives may not be fully effective in the hyperthyroid state because of increased levels of sex hormone–binding globulin and increased clearance of the contraceptive.

21. When is surgery indicated for hyperthyroidism?

Surgery is generally not the treatment of choice for hyperthyroidism. It is most often used in (1) patients with symptomatic compression or large goiters (≥80 g) who are less likely to respond to ATDs or ^{131}I; (2) patients with relatively low RAIU; (3) when thyroid cancer is documented or suspected; (4) patients with large nonfunctioning, photopenic, or hypofunctioning nodules (>4 cm); (5) pregnant patients allergic to or intolerant of ATDs (^{131}I is contraindicated in pregnancy); (6) patients with coexisting hyperparathyroidism requiring surgery; (7) female patients who plan a pregnancy in <6 months provided normal thyroid hormone levels, especially if TSI antibody levels are high; and (8) patients who wish to avoid ^{131}I exposure and potential side effects of long-term ATDs. Surgery may also be preferred when there is moderate to severe active TED, since ^{131}I has been linked to worsening eye disease in these patients. Patients should be euthyroid before surgery (with ATD pretreatment, with or without β-adrenergic blockade) to decrease the risk of arrhythmias and postoperative thyroid storm. Preoperative KI, SSKI, or Lugol's solution is often given prior to surgery to decrease thyroid blood flow, vascularity, and intraoperative blood loss during thyroidectomy (see Question 22).

22. What is the role of iodine in the treatment of hyperthyroidism? What is the Wolff-Chaikoff effect?

Inorganic iodine rapidly decreases the synthesis and release of T_4 and T_3. The transient inhibition of thyroid hormone synthesis by excess iodine is known as the Wolff-Chaikoff effect. However, because escape from this effect often occurs after 10–14 days, iodine is generally used only after ATDs have been started to prepare a patient rapidly for surgery or as an adjunctive measure in patients with thyroid storm. Iodine is also used in some centers to decrease the vascularity of the thyroid prior to thyroidectomy for Graves' disease. Typical doses are Lugol's solution (8 mg iodide/drop) 5–7 drops (0.25–0.35 mL) or saturated solution of potassium iodide (SSKI, 50 mg iodide/drop) 1–2 drops (0.05–0.1 mL) three times daily mixed in water or juice for 10 days prior to surgery.

23. Are other treatments available to lower thyroid hormone levels?

Yes. Two iodine-containing oral cholecystographic agents, ipodate and iopanoic acid, cause dramatic reductions in serum T3 and T4 through the inhibition of T4 5′-monodeiodinase. Neither of these agents is currently available in the United States. Other agents occasionally used to treat hyperthyroidism include lithium, which decreases thyroid hormone release, and potassium perchlorate, which inhibits thyroid uptake of iodine. Cholestyramine interferes with enterohepatic recycling of thyroid hormone and, when given with MMI, lowers serum T4 and T3 more rapidly than MMI alone.

24. Which medications block peripheral conversion of T4 to T3?

PTU, propranolol, glucocorticoids, iopanoic acid, ipodate, tyropanoate, and amiodarone inhibit the peripheral conversion of T4 to T3.

25. How effective are ATDS?

Ninety percent of people taking ATDs become euthyroid without significant side effects. Approximately half of patients attain a remission from Graves' disease after a treatment course of 12–18 months. However, only 30% maintain a long-term remission; the remainder experience recurrence of Graves' disease within 1–2 years after the drugs are withdrawn. Some recent studies have shown the longer the duration of ATD therapy, the higher the likelihood of attaining a remission. TMNG and AFTNs are not autoimmune diseases; therefore, they do not go into remission with ATDs. The role of ATDs in these two disorders is only to render a patient euthyroid before surgery or when pretreatment is necessary before ^{131}I therapy (see Question 27). The usual starting doses for moderate thyrotoxicosis are MMI, 10–20 mg/day, or PTU, 50–150 mg three times/day. MMI is recommended for all patients who select ATD therapy for Graves' disease, except in the clinical circumstances listed in question 20.

26. What side effects are associated with ATDS?

1. Agranulocytosis (defined as granulocyte count <500/uL) is a rare but life-threatening complication of ATD therapy (incidence 0.11–0.27%), occurring in approximately 1 in every 500–900 patients treated with ATDs, usually within 1–3 months of starting ATD. Patients should be instructed to promptly report fever, sore throat, or minor infections that do not resolve quickly. Agranulocytosis appears to be dose related with MMI but not with PTU. People developing agranulocytosis on one ATD should not be exposed to another. Treatment of agranulocytosis should include stopping ATD, broad-spectrum antibiotics, and possible granulocyte colony-stimulating factor administration. Recovery usually occurs within 1–2 weeks, but the condition may be fatal in some severe cases.
2. Hepatotoxicity with occasional progression to fulminant hepatic necrosis can occur with PTU; cholestatic jaundice has been reported with MMI. Recent findings suggested a similar low frequency of cholestatic or hepatocellular hepatotoxicity for both MMI and PTU (0.03%). PTU is more likely to be associated with the need for liver transplant or death than MMI. Patients should be instructed to report right upper quadrant pain, anorexia, nausea, jaundice, light-colored stool or dark urine, and new pruritus while taking ATDs.
3. Rashes occur in approximately 2% of patients (more common with PTU or higher-dose MMI >30 mg/d) and can range from limited erythema to exfoliative dermatitis. Dermatologic reactions to one ATD do not preclude the use of another, although cross-sensitivity occurs in approximately 50% of cases.
4. Arthropathy or a lupus-like syndrome can rarely be seen with either PTU or MMI.

5. Antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis has been associated with PTU use (rarely MMI). Vasculitis may occur at any point during the treatment course. Patients may present with fever, malaise, cutaneous, renal, and pulmonary involvement. Vasculitis usually resolves with ATD discontinuation.
6. Potential teratogenicity (so-called MMI embryopathy) can be associated with MMI; this includes rare fetal scalp defects (aplasia cutis), choanal atresia, omphalocele, omphalomesenteric duct anomaly, patent vitellointestinal duct, and tracheoesophageal fistulas. Mild birth defects, such as preauricular sinuses/cysts and urinary tract abnormalities, can be observed with PTU.
7. Insulin autoimmune syndrome with symptomatic hypoglycemia has rarely been reported with MMI.
8. Baseline blood tests (complete blood count and liver function test) should be obtained before starting ATD therapy. One should reconsider ATD therapy if the baseline absolute neutrophil count is <1000/mm^3 or liver transaminase enzyme levels >5-fold above the upper limit of normal. During ATD treatment, if transaminases increase more than three times the upper limit of normal or worsen from baseline elevation, then ATD should be discontinued.

27. What lab tests should be monitored in patients taking ATDS?

Serum-free T4 and total T3 should be retested about 2 weeks after initiation of an ATD and the dose adjusted accordingly. TSH may remain suppressed for several months, and therefore free T4 and T3 levels are more reliable for assessing thyroid hormone status during this time. Thyroid tests should be monitored thereafter every 4–8 weeks until euthyroidism is achieved with a goal of using the lowest effective ATD dose. Routine monitoring of the white blood count (WBC) and liver function, though commonly done in clinical practice, has not been shown to prevent agranulocytosis or hepatotoxicity. A WBC and differential should be assessed during any febrile illness and at the onset of sore throat/pharyngitis in all patients taking ATDs. Liver function tests should be ordered in patients who experience a pruritic rash, jaundice, light-colored stools or dark urine, arthralgias, abdominal pain or bloating, anorexia, nausea, or fatigue. The ATD therapy should be discontinued if transaminase levels are >3 times the upper limit of normal or progressively increasing from an elevated baseline level. Liver function tests should be monitored every week until the resolution of transaminitis after discontinuing the ATD.

28. How does radioactive iodine work?

Thyroid cells trap and concentrate iodine and use it to make thyroid hormone. ^{131}I is utilized in the same manner as inorganic iodine. Because ^{131}I emits locally destructive beta particles, extensive local thyrocyte damage and ablation of thyroid function occur over a period of approximately 6–18 weeks after treatment. Dosages of ^{131}I should be high enough to cause permanent hypothyroidism and are usually based on the size of the thyroid gland and the pretreatment RAIU. A typical dose for Graves' disease is 10–15 millicuries (mCi); for TMNG, higher doses of 25–30 mCi are often given. These doses are effective in 90–95% of patients.

29. When is pretreatment with ATDs indicated before ^{131}I ablation?

The use of ATDs before and after ^{131}I therapy may be considered in (1) patients who are extremely symptomatic or have free T4 levels that are three to four times the upper normal limit, (2) the elderly, and (3) those with substantial comorbidities such as atrial fibrillation, heart failure, pulmonary hypertension, renal failure, infection, trauma, poorly controlled diabetes mellitus, and cerebrovascular or pulmonary disease. These patients should also be medically stable and treated with beta-adrenergic blocking drugs prior^{131}I therapy.

Pretreatment with ATDs helps deplete the thyroid of preformed hormones and thereby theoretically reduce the risk of ^{131}I-induced thyroid storm. When pretreatment with ATDs is used, the drugs are generally continued until the patient is euthyroid and then discontinued before ^{131}I is given. Abrupt discontinuation of ATDs is associated with a rapid increase in thyroid hormone levels, and therefore current recommendations favor a brief discontinuation of only 2–3 days before ablation therapy is given. Nonpretreated patients usually experience a rapid decrease in thyroid hormone levels after ^{131}I therapy, therefore most otherwise healthy patients do not require or benefit from ATD pretreatment.

30. How long after ^{131}I treatment should women wait before becoming pregnant or resuming breastfeeding?

Pregnancy should be deferred for at least 4–6 months after ^{131}I ablation to ensure successfully cured hyperthyroidism and corrected hypothyroidism prior to conception. In addition, patients should be on a stable dose of thyroid hormone replacement and free of active ophthalmopathy. Breast milk radioactivity, measured in one study after an 8.3 mCi therapeutic dose of ^{131}I, remained unacceptably high for 45 days, prohibiting the resumption of breastfeeding after ^{131}I therapy. If ^{99m}Technetium or ^{123}I is used for diagnostic studies, breastfeeding may be resumed in 2–3 days, with pumping and disposal of breast milk in the interim.

31. Does ^{131}I cause or worsen orbitopathy in Graves' disease?

The natural history of Graves' disease is such that up to 25% of patients develop clinically apparent orbitopathy, but fewer than 5% develop severe eye involvement. The majority of orbitopathy cases arise in the period from 18 months before to 18 months after the onset of thyrotoxicosis. Thus, a fair number of new cases can be expected to coincide with the timing of ^{131}I ablation. However, three randomized clinical trials have shown that ^{131}I therapy is more likely to be associated with new or worsened orbitopathy compared with either ATDs or thyroidectomy. ^{131}I therapy results in a sustained increase in TSH receptor antibodies that may be important in exacerbating orbitopathy. Patients with preexisting eye disease, those who smoke cigarettes, and those with higher levels of thyroid hormone and high titers of TSH-receptor antibodies are more likely to experience worsening. It is therefore prudent to avoid ^{131}I in patients with active moderate-to-severe TED. In patients with initially mild eye involvement, concurrent use of oral glucocorticoids can be used to prevent an exacerbation during ^{131}I therapy, particularly in the presence of other risk factors for worsening orbitopathy.

32. How is thyrotoxicosis managed in pregnancy?

Caution must be used in interpreting thyroid laboratory results during pregnancy, because low TSH values are not uncommon in the first trimester, and total T4 and total T3 levels are elevated by increased thyroxine-binding globulin (TBG) levels. Free T4 levels, using equilibrium dialysis or an assay with trimester-specific reference ranges, are the best indicator of thyroid function during pregnancy. Symptomatic women with marked elevation in trimester-specific free T4 levels or those with total T4 and/or total T3 above 1.5 times the upper normal limit should be considered for treatment. Pregnant women with subclinical hyperthyroidism (low TSH, normal free T4) and asymptomatic or mild hyperthyroidism may be monitored without treatment by measuring TSH and free T4 every 4–6 weeks. Beta-adrenergic blockers (propranolol or metoprolol, but not atenolol) can be used cautiously and should be weaned once hyperthyroidism is controlled by ATDs because of the risks of fetal growth restriction, hypoglycemia, respiratory depression, and bradycardia. Nuclear medicine testing with RAIU or thyroid scanning is contraindicated in pregnancy due to the risk of fetal exposure to isotopes. Because ^{131}I therapy is also contraindicated during pregnancy, treatment options are limited to ATDs or surgery. The ATA and the US Food and Drug Administration (FDA) recommend that PTU be used in the first trimester, due to the potentially serious teratogenic effects of MMI during organogenesis of the first trimester (aplasia cutis, choanal atresia, and tracheoesophageal fistulas). Upon reaching the second trimester, patients are frequently switched to MMI, but alternatively, PTU may be continued if concerns about loss of control are deemed to outweigh the risk of hepatic dysfunction. A 300-mg daily dose of PTU (in three divided doses) is roughly equivalent to a 10- or 15-mg daily MMI dose. Thyroid function tests should be obtained 2–4 weeks after switching ATDs to ensure maintenance of euthyroidism. The lowest possible dose of ATD should be used to keep the mother's thyroid hormone levels at or slightly above the reference range and TSH slightly suppressed. Pregnant patients with Graves' disease require close follow-up to ensure adequate control and to prevent hypothyroidism due to overtreatment with ATDs, because Graves' disease frequently remits during the course of pregnancy. TSH receptor antibodies, which cross the placenta after 26 weeks, should be measured at the time of diagnosis of pregnancy and if elevated, should be repeated at 18–22 weeks, and again at 30–34 weeks of gestation to assess the risk of neonatal thyroid dysfunction. Fetal assessment should include monitoring for tachycardia in mothers with persistent elevations in TSH receptor antibodies, and fetal ultrasound to assess for evidence of fetal goiter or growth restriction.

Surgery (thyroidectomy) should only be performed when medical management has been unsuccessful or ATDs cannot be used. Whenever possible, surgery should be confined to the second trimester because of teratogenic effects associated with anesthetic agents increased risk of fetal loss in the first trimester, and the increased risk of preterm labor in the third trimester.

33. What are the treatments for thyroid eye disease?

People with TED should be treated according to the severity of their eye involvement. The general approach to treatment includes reversal of hyperthyroidism, smoking cessation, and reduction of ocular surface irritation and periorbital inflammation. Those with only mild eye involvement may generally be treated with local measures and lifestyle intervention, such as tinted lenses for photosensitivity, lubricants, artificial tears (methylcellulose eye drops), selenium supplements, raising the head of the bed to prevent worsening retroocular edema in the recumbent position overnight, and eye patching or prisms for diplopia. Active, moderate eye involvement with lid erythema and edema, conjunctival erythema and edema (chemosis) often responds to intravenous glucocorticoid therapy (IVGC). A typical regimen is a methylprednisolone 0.5 g IV weekly for 6 weeks followed by 0.25 g weekly for 6 additional weeks. IVGC is preferred for active, moderate-to-severe TED when disease activity is prominent without significant proptosis or diplopia. Teprotumumab, rituximab, mycophenolate, and tocilizumab may be considered in glucocorticoid-resistant patients with active moderate-to-severe TED. Teprotumumab, a monoclonal antibody to the IGF-1 receptor approved by the FDA for patients with TED in 2020, is a preferred treatment in those with active moderate-to-severe TED with significant proptosis and/or diplopia. Sight-threatening orbitopathy is a medical emergency, occurring as a result of optic nerve compression by enlarged extraocular muscles at the apex of the orbit, or because of corneal ulceration. In the former case, pulse intravenous glucocorticoids should be given immediately, and patients should be admitted to the hospital for possible urgent orbital decompression surgery if no response to IVGC is seen within 1–2 weeks.

KEY POINTS

Hyperthyroidism

- The three most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and toxic adenoma.
- Thyroiditis can cause severe thyrotoxicosis but generally resolves without intervention and may be followed by a hypothyroid phase.
- Routine diagnostic testing for hyperthyroidism includes TSH, free T4, and T3. The diagnosis may be confirmed with RAIU and thyroid radionuclide scanning, measurement of TSH-receptor antibodies, or with the use of color-flow Doppler in experienced hands.
- The major treatment choices for hyperthyroidism are radioiodine, antithyroid drugs (usually methimazole), and thyroidectomy. Beta-blockers can significantly improve adrenergic symptoms of thyrotoxicosis and do not interfere with testing or later treatment.
- Treatment is generally indicated in all patients when TSH is less than 0.1 mU/L.
- General treatment of patients with thyroid eye disease includes reversal of hyperthyroidism, monitoring for and prompt treatment of hypothyroidism, and smoking cessation.
- Medical therapies for Graves's orbitopathy may include glucocorticoids, teprotumumab, mycophenolate, selenium, rituximab, or tocilizumab.
- Surgery may be required in the case of compressive optic neuropathy or sight-threatening.

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CHAPTER 41

Hypothyroidism

Caitlin C. Bell and Bryan R. Haugen

1. What is hypothyroidism?

Hypothyroidism is a condition that results from inadequate production or action of thyroid hormone, most commonly due to primary hypothyroidism or failure of the thyroid gland itself. Hypothyroidism can be overt, with a frank decrease in serum thyroxine (T4) levels and a compensatory increase in thyroid-stimulating hormone (TSH) levels. It more commonly presents as subclinical hypothyroidism (also called *mild thyroid failure*), in which the TSH is mildly elevated but T4 levels are within the reference range. Subclinical hypothyroidism often presents with few or no symptoms, but hypercholesterolemia and subtle cardiac abnormalities can be seen (Fig. 41.1).

2. How common is hypothyroidism?

Hypothyroidism is a common condition. The prevalence of hypothyroidism is rising and is estimated to be 9.65–11.7% in the United States. The prevalence of overt hypothyroidism is estimated at 0.3–3.7% and subclinical hypothyroidism at 4–8%. Increasing prevalence may be due to an aging population, increased TSH screening, and a lower threshold to start levothyroxine therapy. The mean age at diagnosis is the mid-50s. Hypothyroidism is much more common in women, with a female-to-male ratio of 2–3:1. Postpartum hypothyroidism, a transient hypothyroid phase after pregnancy, occurs in 5–10% of women.

3. What are the two most common causes of hypothyroidism?

Although many disorders can cause hypothyroidism, the two most common causes in the United States are chronic lymphocytic thyroiditis (Hashimoto's disease), an autoimmune form of thyroid destruction, and radioiodine-induced hypothyroidism after treatment of Graves' disease (autoimmune hyperthyroidism). Severe iodine deficiency is the most common cause worldwide.

4. List the less common causes of hypothyroidism.

- Thyroidectomy
- Thyroiditis (viral, postpartum, silent)
- External irradiation to the neck
- Medications (antithyroid drugs, amiodarone, lithium, bexarotene, tyrosine kinase inhibitors, immune checkpoint inhibitors, and interferon)
- Infiltrative diseases
- Central (pituitary/hypothalamic) hypothyroidism
- Congenital defects
- Endemic (iodine-deficient) goiter, which is common outside the United States

5. List the symptoms commonly experienced in hypothyroidism.

Hypothyroidism commonly presents with nonspecific symptoms such as fatigue, cold intolerance, depression, difficulty concentrating, weight gain, weakness, joint aches, constipation, dry skin, hair loss, and menstrual irregularities.

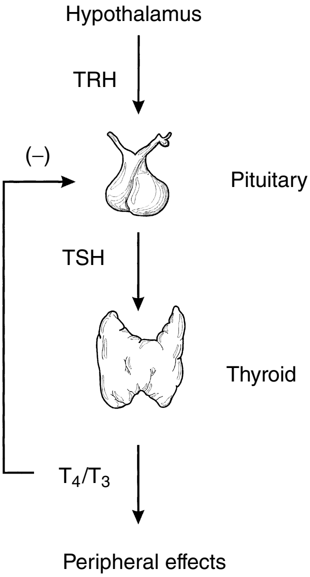

Fig. 41.1 Hypothalamic–pituitary–thyroid axis. *T3*, Triiodothyronine; *T4*, thyroxine; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone.

6. What findings on physical examination are consistent with hypothyroidism?

Physical examination may be normal with mild thyroid failure and should not deter further workup if clinical suspicions are high. Common signs of moderate-to-severe hypothyroidism include:

- Hypertension (diastolic hypertension is a clue)
- Bradycardia
- Coarse hair
- Periorbital swelling
- Yellow skin (caused by elevated levels of beta-carotene)
- Carpal tunnel syndrome
- Delayed relaxation of the deep tendon reflexes

7. What does palpation of the thyroid reveal?

The thyroid may be enlarged, normal, or small in hypothyroidism, but thyroid consistency is usually firm.

8. Summarize the unusual presentations of hypothyroidism.

The unusual presentations of hypothyroidism include megacolon, pericardial effusion, cardiomegaly, and congestive heart failure (CHF). In one reported case, the patient was scheduled for cardiac transplantation for severe CHF, but before transplantation could be undertaken, the CHF resolved with thyroid hormone replacement alone.

9. Describe the laboratory tests that may be abnormal during hypothyroidism.

Laboratory clues to overt hypothyroidism include normochromic, normocytic anemia (menstruating women may also have iron-deficiency anemia caused by excessive bleeding resulting from irregular menses), hyponatremia, hypoglycemia, hypercholesterolemia, and elevated levels of creatine phosphokinase.

10. What tests best confirm the diagnosis of hypothyroidism in the outpatient setting?

Many thyroid function tests are available to the clinician, including assessments of TSH, T4, triiodothyronine (T3), T3 resin uptake (T3RU), free T4, free T3, and reverse T3 (RT3). In the outpatient setting, measurement of serum TSH is usually sufficient. TSH, which is synthesized and secreted from the anterior pituitary gland, is the most sensitive indicator of thyroid function in the nonstressed state. If the TSH is normal (reference range: 0.45–4.5 mU/L), the patient is euthyroid; if the TSH is elevated (>4.5 mU/L), the patient has primary gland failure. In the unusual case where central hypothyroidism is suspected, a free T4 is the best screening test.

11. How should total T4 levels be interpreted?

Care must be taken in interpreting total T4 levels (occasionally performed on health screening panels). Many conditions unrelated to thyroid disease cause low or elevated levels of total T4 because >99% of T4 is protein bound, and thus total T4 levels depend on the amount of thyroid-binding proteins, which may vary greatly. Total T4 levels must always be interpreted with the T3RU or thyroxine-binding globulin (TBG), which reflects the amount of thyroid hormone–binding protein.

12. Explain why thyroid function tests are more difficult to interpret in acutely ill inpatients.

Interpretation of thyroid function tests in acutely ill inpatients is more difficult when hypothyroidism is suspected. Acute nonthyroidal illness (also known as euthyroid sick syndrome) may cause reversible suppression of the total T4, free T4, total T3, free T3, and TSH levels; TSH may then be elevated in the recovery phase (see Chapter 46). Medications, such as dopamine and glucocorticoids, may also suppress the TSH. Therefore, TSH should only be checked in hospitalized patients when the clinical suspicion for hypothyroidism is high.

13. How do you diagnose hypothyroidism in acutely ill inpatients?

When hypothyroidism is suspected in the stressed, hospitalized patient, a combination of clinical signs (inappropriate bradycardia, puffy facies, dry skin, and delayed relaxation of deep tendon reflexes) and laboratory tests (TSH and free T4 levels) is necessary to exclude or confirm the diagnosis of hypothyroidism. If these tests are equivocal, the RT3 level, which is normal or elevated in nonthyroidal illness and low in hypothyroidism, may prove helpful. Inpatient TSH testing also may be confounded by normal diurnal variations in TSH. TSH levels in euthyroid individuals may exceed the reference range at night when patients are frequently admitted. A morning test may help clarify the significance of a mildly elevated TSH.

14. Who should be treated for hypothyroidism?

All patients with overt hypothyroidism should be treated. Not all patients with subclinical hypothyroidism will have symptomatic improvement with treatment, particularly if they have mild symptoms or mild elevations in TSH. Treatment for subclinical hypothyroidism is generally recommended for patients younger than 70 who have persistent TSH levels >10 mU/L, particularly for those with cardiac and lipid abnormalities. Treatment for subclinical hypothyroidism where the TSH is only mildly elevated (5–10 mU/L) and/or the patient is older than 70 should be based on clinical judgment. In this case, it may be helpful to check thyroid peroxidase antibodies to help predict which patients will likely progress to overt hypothyroidism.

15. Which thyroid hormone preparation should you use?

Since 1891, when sheep thyroid extract was first used to treat myxedema, many preparations have been developed and are still available. Currently, the best replacement regimen is levothyroxine (LT4).

16. What other thyroid hormone preparations are available?

Other thyroid hormone preparations include liothyronine (LT3), which is reserved for special cases because of its potency and short half-life, and desiccated thyroid extracts (DTE), which give unpredictable serum thyroid hormone concentrations because of variable content and bioavailability. DTE is also a porcine extract, and the ratio of T4:T3 (5:1) is different from the human thyroid (10–14:1).

17. What is the recommended dose of LT4 for replacement therapy in a patient with hypothyroidism?

Healthy, young patients with overt hypothyroidism may be started on full replacement doses of LT4 (1.6 mcg/kg/day). Elderly patients and those with known or suspected cardiac disease should be started on low LT4 doses (25–50 mcg/day), which are increased by 25 mcg/day every 4–6 weeks until the TSH reaches normal levels. In patients with subclinical hypothyroidism, consider starting the patient on 50–75% of the predicted full replacement dose. In obese patients, it is helpful to calculate the starting levothyroxine dose based on ideal body weight as opposed to actual body weight. Recently, computer-assisted LT4 dose calculators have included age, sex, weight, and use of supplemental calcium; these calculators have been shown to be more accurate than the weight-based calculations alone.

18. What is the appropriate goal for TSH in the treatment of primary hypothyroidism?

Traditionally, the target TSH level in treated hypothyroid patients has been 0.5–2.5 mU/L, representing the lower end of the normal range reported by most laboratories (0.5–5 mU/L). When these “normal” TSH reference ranges were developed, they included subjects with antithyroid antibodies suggestive of occult autoimmune thyroid disease. The “normal” ranges are, therefore, thought to be skewed toward higher TSH values. When normal subjects with no antithyroid antibodies are evaluated, most have TSH values <2.5 mU/L. However, there is little data to support the idea that a low-normal TSH is clinically superior to a TSH in the normal to high-normal reference range.

19. Discuss the evidence supporting combination T4/T3 therapy.

The medical and lay literature has taken a renewed interest in combination therapy. Animal studies have shown that T4 therapy alone does not restore tissue levels of both T4 and T3 to euthyroid levels, even when the TSH level is normalized. Some hypothyroid patients continue to report symptoms despite normal TSH values on LT4 alone. Although these observations are provocative, most studies evaluating combination therapy, including a large meta-analysis, have shown no demonstrable difference in symptoms or weight with LT4 monotherapy versus combination therapy. However, some patients in the studies did report a preference for combination therapy despite a lack of objective measurable benefit. Most experts agree that more information is needed before combination T4/T3 therapy can be recommended for most patients. Our current approach is to discuss this information openly with inquiring patients.

20. When should you consider combination T4/T3 therapy?

We suggest a trial of LT4 alone to normalize TSH within the low-normal range (0.5–2.5 mU/L) for a period of 2–4 months. Many patients do extremely well with this approach. Patients who have low-normal TSH while taking LT4 and still feel "hypothyroid" require further evaluation before LT3 therapy is considered. We generally exclude anemia and vitamin B12 deficiency (associated with Hashimoto's thyroiditis) and inquire about sleep apnea and depression. If this assessment is negative, we decrease the LT4 by 12–25 mcg and add 5 mcg of liothyronine (LT3) in the morning. The goal is to determine whether the patient's symptoms improve without persistent suppression of the serum TSH (measured in the morning before taking medication). We discussed with the patient that if they do not feel a significant benefit to combination T4/T3 therapy after 3 months, we will move them back to LT4 monotherapy. There is no data to clearly support or refute this position; we believe that it is a position of "good" medical practice.

21. What are the consequences of treating hypothyroid patients with excess doses of thyroid hormone?

The consequences of overtreatment of hypothyroidism can be both acute and chronic. Acute complications include symptoms of thyrotoxicosis: anxiety, tremors, palpitations, insomnia, and so on. Chronic complications of thyroid hormone excess that are well documented include a significantly increased risk of atrial fibrillation, osteoporosis with skeletal fractures, and premature mortality. These risks are especially high in patients age >60 years.

22. How should the clinician approach surgery in a patient with hypothyroidism?

There are two broad categories to consider: emergent/cardiac surgery and elective surgery. Hypothyroidism is associated with minor postoperative complications—gastrointestinal (prolonged constipation, ileus), as well as neuropsychiatric symptoms (confusion, psychosis); in addition, the incidence of fever in response to infections is lower. Patients scheduled for elective surgery should wait until the TSH level is normalized because of the potential postoperative complications associated with hypothyroidism. However, rates of mortality and major complications (blood loss, arrhythmias, and impaired wound healing) are similar to the rates in euthyroid patients.

23. Summarize the current recommendations for emergent surgery.

Current recommendations are to proceed with emergent surgery in the hypothyroid patient and to monitor for potential postoperative complications while giving replacement therapy with LT4. Patients with ischemic coronary artery disease requiring surgery should proceed without LT4 replacement because T4, if given before surgery, increases myocardial oxygen demands and may precipitate worsening cardiac symptoms. Postoperatively, the patient should receive replacement therapy with LT4 at a slow rate and be monitored for CHF (the risk for which is increased in patients with hypothyroidism undergoing cardiac surgery).

24. How does myxedema differ from hypothyroidism?

Myxedema is a severe, uncompensated form of prolonged hypothyroidism. Complications include hypoventilation, cardiac failure, fluid and electrolyte abnormalities, hypothermia, and coma (see Chapter 45). Myxedema coma is frequently precipitated by an intercurrent systemic illness, surgery, or narcotic/hypnotic drugs. Patients with myxedema coma should receive replacement therapy with 200–500 mcg of intravenous LT4, followed by weight-based replacement each day. Because conversion of T4 to T3 (active hormone) is decreased with severe illness, patients with profound cardiac failure that requires pressors or patients unresponsive to 1–2 days of LT4 therapy can be given a loading dose of 5–20 mcg LT3 intravenously, followed by 2.5–10 ug every 8 hours.

KEY POINTS

Hypothyroidism

- TSH test is the best screening test for primary hypothyroidism in the outpatient setting.
- Levothyroxine administration is the preferred initial treatment for hypothyroidism and in healthy young patients can be started at a dose of 1.6 mcg/kg/day.
- The goal TSH for treatment of primary hypothyroidism is 0.5–2 mU/L.
- Subclinical hypothyroidism (also called mild thyroid failure, elevated TSH but normal thyroxine/triiodothyronine) is common; treatment can improve symptoms as well as cardiac and lipid abnormalities.

WEBSITE

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Thyroiditis

Jill K. Wagoner, Ayesha F. Malik, Robert C. Smallridge, and Ana Chindris

1. What is thyroiditis?

Thyroiditis is an inflammation of the thyroid that can be caused by various conditions. Destructive thyroiditis, which includes acute, subacute, postpartum, and painless thyroiditis, involves a transient destruction of thyroid follicles that leads to the release of excessive amounts of T4 and T3 into the circulation. This type of thyrotoxicosis is not treated with antithyroid drugs; instead, management focuses on pain and symptom control. Thyroid hormone abnormalities may or may not resolve with time. Hashimoto's thyroiditis, an autoimmune disorder, is characterized by lymphocytic infiltration and a progressive course toward hypothyroidism. Other causes include certain drugs, Riedel's struma, radiation, and trauma.

2. Give the differential diagnosis for thyroiditis.

1. Infectious
    b. Acute (suppurative)
    c. Subacute (also known as granulomatous, nonsuppurative, or de Quervain's)
2. Autoimmune
    c. Chronic lymphocytic (Hashimoto's)
    d. Atrophic
    e. Immunoglobulin G4 (IgG4)
    f. Juvenile (goitrous or atrophic)
    g. Postpartum
3. Painless (nonpostpartum)
4. Drug-induced (lithium, amiodarone, tyrosine kinase inhibitors, checkpoint inhibitor immunotherapy, iodinated contrast material)
5. Riedel's struma (fibrous)
6. Radiation-induced (^{131}I and external radiation)
7. Trauma or palpation-induced
8. Tumor embolization

3. How does acute thyroiditis present and what causes it?

Affected individuals may present with anterior neck pain following a respiratory infection. It sometimes presents with symptoms of thyrotoxicosis or abnormal thyroid hormone levels.

This rare disease has an infectious etiology with the most commonly reported pathogens being *Staphylococcus, Streptococcus,* and *Mycobacterium* species. Fungal, parasitic, or syphilitic infections have been reported, and immunocompromised persons may be at increased risk. Rarely, metastatic disease to the thyroid gland can present as acute thyroiditis.

4. How is acute thyroiditis managed?

Treatment involves incision and drainage of the abscess or surgical excision and antimicrobials. Children often have a pyriform sinus fistula, which should be surgically repaired.

5. What causes subacute thyroiditis?

Subacute thyroiditis is a self-limited granulomatous inflammation probably viral in origin. Agents implicated include the mumps virus, coxsackie virus, influenza, and adenoviruses. Although people almost always recover clinically, serum thyroglobulin (Tgb) levels remain elevated, and intrathyroidal iodine content is low for many months (Fig. 42.1). Such findings suggest persistent subclinical abnormalities after an episode of subacute thyroiditis. Up to 4% of affected individuals have a second episode many years later.

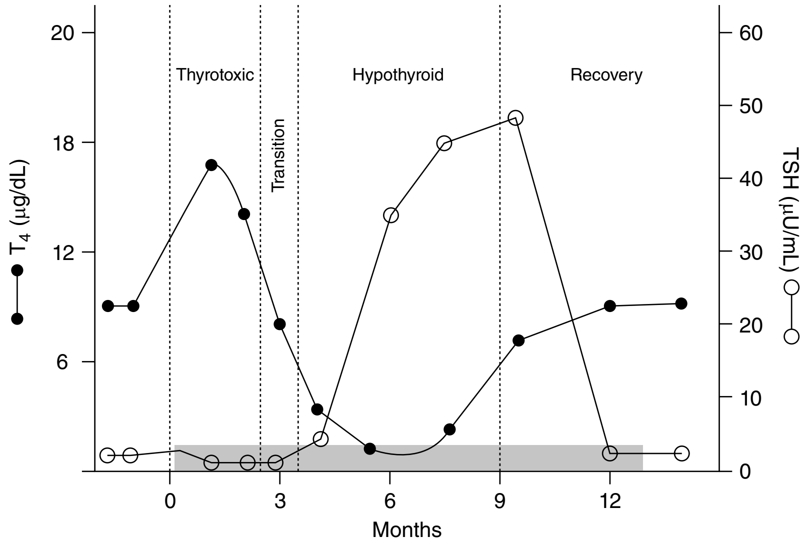

Fig. 42.1 Thyroid function during subacute thyroiditis.

6. Describe the four stages of subacute thyroiditis.

- *Stage I:* Pain and unilateral or bilateral tenderness of the thyroid that may radiate to the ears or jaw. Systemic symptoms (fatigue, malaise, fever) may be present. Inflammatory destruction of thyroid follicles permits the release of thyroxine (T4) and triiodothyronine (T3) into the circulation, and thyrotoxicosis may ensue.
- *Stage II*: A transitory period (several weeks) of euthyroidism occurs after the T4 is cleared from the body.
- *Stage III*: With severe disease, people may become hypothyroid until the thyroid gland repairs itself.
- *Stage IV*: Euthyroid state usually returns, but 5–15% remain hypothyroid.

7. How is subacute thyroiditis managed?

The primary goal is to reduce both thyroid inflammation and symptomatic tachycardia. Nonsteroidal anti-inflammatory agents are first-line treatment in mild to moderate cases, whereas steroids may be needed when the condition is more severe. Individuals requiring steroids are more likely to become hypothyroid at a later time. Thyroid hormone replacement is indicated in the 5–15% who remain hypothyroid following resolution of thyroiditis. Tachycardia related to T4 and T3 release can be controlled with beta-blockade.

8. What is the most common cause of thyroiditis?

Autoimmune thyroid disease is recognized by the presence of thyroid peroxidase (TPO) antibody and, less frequently, thyroglobulin antibody in serum. The prevalence of these antibodies is about 10% in reproductive-age women, about 19% in older women, and 5% in men.

9. Describe the clinical characteristics of autoimmune thyroid disease.

Chronic lymphocytic thyroiditis (Hashimoto's disease) usually presents as a euthyroid goiter in a female. It progresses to hypothyroidism at a rate of 5% per year. Progressive disease may lead to a small thyroid gland causing atrophic thyroiditis. Some evidence suggests that thyroid growth inhibitory antibodies may account for the lack of a goiter in atrophic thyroiditis. Those with juvenile thyroiditis usually present with a goiter. IgG4 thyroiditis is thought to be on the spectrum of Hashimoto's thyroiditis and is characterized by a greater degree of stromal fibrosis, lymphoplasmacytic infiltration, and hypothyroidism.

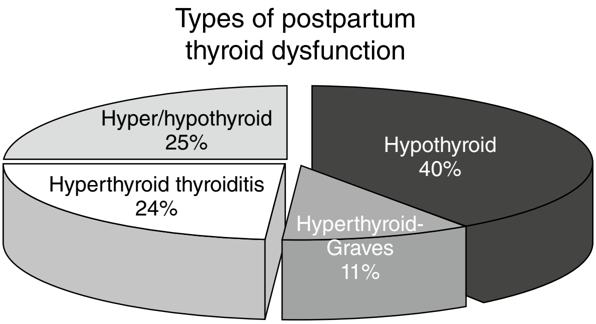

Fig. 42.2 Frequency of clinical presentations of postpartum thyroiditis.

TABLE 42.1 Subacute Versus Postpartum Thyroiditis

	SUBACUTE THYROIDITIS	POSTPARTUM THYROIDITIS
Thyroid pain	Yes	No
Sedimentation rate	Increased (>50 mm/hr)	Normal
TPO antibody	Transient increase only	Positive
HLA status	B-35	DR3, DR5
Histology	Giant cells, granulomas	Lymphocytes

HLA, human leucocyte antigen; *TPO*, thyroid peroxidase.

10. Does postpartum thyroiditis follow a different clinical course from other types of autoimmune thyroiditis?

Yes. Postpartum disease develops in women between the third and ninth months after delivery, rarely up to 1 year postpartum. It typically follows the stages seen with subacute thyroiditis, although histologically there is lymphocytic infiltration rather than granulomatous inflammation.

11. How common is postpartum thyroiditis?

After delivery, 5–10% of women develop biochemical evidence of thyroid dysfunction.

Approximately one-third of affected women develop symptoms (either thyrotoxicosis, hypothyroidism, or both) and benefit from 6–12 months of therapy with L-thyroxine (L-T4) if hypothyroid. Up to 70% of women will develop recurrence with subsequent pregnancies. The frequency of each clinical presentation is depicted in Fig. 42.2.

12. Which women with postpartum thyroiditis should be treated?

Postpartum thyroiditis is a destructive process releasing preformed thyroid hormone; therefore, antithyroid drugs (methimazole or propylthiouracil) are not effective. If thyrotoxic symptoms are present, beta-blockers can be used. Hypothyroid women with severe symptoms and those who desire conception should receive treatment with L-T4. In these cases, however, tapering off the medication should be tried 6–12 months after initiation, in the attempt to eventually discontinue therapy.

13. Summarize the differences between subacute and postpartum thyroiditis.

See Table 42.1.

14. Why do women develop postpartum thyroiditis?

Women who develop postpartum thyroiditis have underlying, usually asymptomatic, autoimmune thyroiditis. During pregnancy, the maternal immune system is partially suppressed, with a dramatic rebound rise in thyroid antibodies after delivery. Although TPO or thyroglobulin antibodies are not believed to be cytotoxic, they are currently the most reliable marker of susceptibility to postpartum disease.

15. Does thyroid function in Women with postpartum thyroiditis return to normal, as it does in subacute thyroiditis?

Not always. Approximately 20% of women become permanently hypothyroid, and a similar number have persistent mild abnormalities. An annual TSH test is therefore recommended.

16. What factors identify women at increased risk for developing postpartum thyroiditis?

Women with a higher TPO antibody titer are more likely to develop postpartum thyroiditis. Approximately 25% of women with type 1 diabetes mellitus develop thyroiditis after delivery. For high-risk individuals, screening for thyroid antibodies and careful monitoring of thyroid function at 3–6 months postpartum are indicated.

17. What is painless thyroiditis?

Both men and non-postpartum women may present with transient thyrotoxic symptoms. As with subacute thyroiditis, they often experience subsequent hypothyroidism. Unlike subacute disease, this disorder is painless. It has been given a variety of names, including hyperthyroidism, silent thyroiditis, transient painless thyroiditis with hyperthyroidism, and lymphocytic thyroiditis with spontaneously resolving hyperthyroidism. This disease was first described in the 1970s and reached its peak incidence in the early 1980s. It seems to occur less often now.

18. What causes painless thyroiditis?

Some investigators believe that it is a variant of subacute thyroiditis because a small percentage of people with biopsy-proven subacute (granulomatous) disease have had no pain (they may have fever and weight loss and may be mistaken for having systemic disease or malignancy). Others believe that it is a variant of Hashimoto's disease because of similar lymphocytic histology. Hashimoto's thyroiditis can occasionally present with thyroid pain; rarely surgery is necessary to relieve symptoms.

19. What is the natural history of painless thyroiditis?

It is similar to the stages of subacute thyroiditis. It may present with thyrotoxicosis in the first 6 weeks, followed by 4 weeks of a euthyroid state, another 4–6 weeks of hypothyroidism, and ultimately a return to the euthyroid state.

20. When a person presents with thyrotoxic symptoms, an elevated free T4 level, and a suppressed TSH, what test should be ordered next?

Measurement of thyrotropin receptor antibodies (TRAb) or thyroid-stimulating immunoglobulins (TSI) is a good place to start. Unequivocally elevated TRAb or TSI indicates that Graves's disease is the likely cause. However, mildly positive TRAb and TSI titers have been reported in some cases of destructive thyroiditis. If TRAB and/or TSI are negative or mildly positive, a 24-hour radioactive iodine uptake (RAIU) should be performed. When the thyroid is overactive (Graves' disease or toxic nodular disease), the RAIU is elevated. In destructive thyroiditis, the RAIU is low due to suppression of TSH by the acutely increased level of serum T4 and the diminished ability of damaged thyroid follicles to trap and organify iodine.

21. What is the appropriate therapy for persons with any type of destructive thyroiditis?

In the thyrotoxic stage, beta-blockers relieve adrenergic symptoms. All forms of antithyroid therapy (drugs, radioactive iodine ablation, and surgery) are absolutely contraindicated. NSAIDs or aspirin may provide prompt relief of thyroid pain. If there is no improvement in 2 to 3 days, the NSAID should be discontinued and prednisone 40 mg daily should be started. Some studies have also shown improvement with prednisolone 15 mg daily. For the hypothyroid phase, thyroid hormone may be used to relieve hypothyroid symptoms and should be continued for 6–12 months, depending on the severity of the disease. Some individuals require no therapy.

22. Which drugs can induce thyroiditis?

Amiodarone, an iodine-containing antiarrhythmic drug, may cause thyroid damage and thyrotoxicosis in about 5–20% of cases by inhibitory or cytotoxic mechanisms or precipitation of underlying autoimmune disease.

Lithium therapy used for bipolar disease has been associated with granulomatous thyroiditis, as well as with destructive thyroiditis without lymphocytic infiltration causing hypothyroidism more commonly than thyrotoxicosis.

Checkpoint inhibitor immunotherapies (ipilimumab, nivolumab, pembrolizumab, atezolizumab) are commonly used for metastatic melanoma and multiple other malignancies. They have been found to cause many endocrinopathies including hypophysitis, thyrotoxicosis, and destructive thyroiditis causing hypothyroidism.

Tyrosine kinase inhibitors (e.g., sunitinib, sorafenib, cabozantinib) have been noted to cause hypothyroidism in 50–70% of patients, potentially by causing destructive thyroiditis. Thyrotoxicosis has also been reported.

Interferon alpha, used commonly for the treatment of hepatitis C (less commonly, interferon beta), and interleukin-2, used for metastatic cancer and leukemia (e.g. denileukin difitox), can cause both hyper- and hypothyroidism.

Nonionic contrast materials (e.g., Hexabrix) were reported to cause destructive thyroiditis.

23. How does amiodarone-induced thyroiditis present?

Amiodarone contains 37% iodine by weight, and about 3000 mcg of iodine is released into the systemic circulation per 100 mg of amiodarone. The daily recommended iodine allowance is 150 mcg for men and nonpregnant women and 220 mcg for pregnant women. Because of the large amount of iodine in this drug, it can cause either hypothyroidism or thyrotoxicosis. Distinguishing thyrotoxicosis due to iodine excess (type 1 disease) from amiodarone-induced destructive thyroiditis (type 2 disease) can be difficult. Some differentiating features are listed in Table 42.2. The absence of blood flow on Doppler sonography is particularly helpful in confirming type 2 disease.

24. What is Riedel's Struma?

Riedel's struma is a rare IgG4–related disorder in which the thyroid becomes densely fibrotic and hard. Local fibrosis of adjacent tissues may produce obstructive symptoms that require surgery. In some cases, fibrosis of other tissues (fibrosing retroperitonitis, orbital fibrosis, or sclerosing cholangitis) may occur.

25. How is Riedel's thyroiditis treated?

Surgical removal of the thyroid isthmus may relieve constrictive symptoms. Glucocorticoids have been helpful, as has tamoxifen, which inhibits fibroblast growth by stimulating transforming growth factor-β. Treatment with a combination of mycophenolate mofetil and prednisone has been reported.

26. Are there any other causes of thyroiditis?

Yes. High-dose external radiation can cause painless thyrotoxic thyroiditis. Various forms of neck trauma (neck surgery, cyst aspiration, seatbelt injury) and tumor emboli have also been reported. Infiltration by sarcoidosis or amyloid may also cause thyroiditis.

TABLE 42.2 Type 1 Versus Type 2 Amiodarone Induced Thyroiditis

	TYPE 1	TYPE 2
Thyroid size	Goiter; nodules	Normal
RAIU	↓, normal, ↑	↓↓
Thyroid antibodies	↑, negative	Negative
Interleukin-6	Normal, ↑	↑↑
Ultrasound Doppler flow	↑	↓
Therapy	Antithyroid drugs, potassium perchlorate; thyroidectomy	Antithyroid drugs (?), steroids

RAIU, radioactive iodine uptake; ↓, low; ↑, high; ↓↓, very low; ↑↑, very high.

KEY POINTS

Thyroiditis

- In early subacute thyroiditis, the RAIU is suppressed, and the sedimentation rate is markedly elevated.
- Approximately 10% of premenopausal women are TPO-antibody positive; many develop postpartum thyroid dysfunction.
- Amiodarone-induced thyroid disease (AITD) may be due to iodine-induced thyrotoxicosis (type 1 AITD) or destruction-induced thyroiditis (type 2 AITD).
- Subacute thyroiditis may require analgesics (or steroids) and beta-blockers early and l-thyroxine (L-T4) during recovery but usually resolves.
- Acute infectious thyroiditis requires prompt incision and drainage and antimicrobial therapy.

WEBSITE

http://www.thyroidmanager.org

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Thyroid Nodules and Goiter

Caitlin C. Bell and Sarah E. Mayson

CHAPTER 43

1. What is a thyroid nodule?

A thyroid nodule is a lesion or growth in the thyroid gland that is radiographically distinct from the surrounding thyroid parenchyma on ultrasound. It may or may not be palpable on clinical exam. The differential diagnosis of a thyroid nodule includes both benign and malignant etiologies. Benign lesions include thyroid follicular nodular disease, pure cysts, nodules related to Hashimoto's thyroiditis, and follicular and oncocytic adenomas. Thyroid nodules can also represent nonthyroidal lesions (e.g., parathyroid adenoma or paraganglioma). Malignant lesions constitute only a small percentage of all thyroid nodules. Differentiated thyroid cancer represents the most common type of thyroid malignancy, accounting for >90% of all thyroid cancers, and includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and oncocytic carcinoma of the thyroid. Less common malignancies include medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, primary thyroid lymphoma, and metastatic cancers of nonthyroidal origin (e.g., breast, renal cell). Nodules that are currently classified as noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) were previously considered under the follicular variant of PTC umbrella. These neoplasms were reclassified as a nonmalignant histologic diagnosis in 2017 to reflect their clinically indolent behavior and extremely low risk of metastasis.

2. How common are thyroid nodules?

Thyroid nodules are common, but the prevalence depends on the population studied and the methods used to detect them. The prevalence of thyroid nodules discovered on palpation is 4–5%; however, the prevalence increases to 50–67% if determined by ultrasonography or at autopsy. Nodules are more common with increasing age, in women, in those living in geographical areas with iodine deficiency, and in individuals exposed to ionizing radiation.

3. What is a goiter?

A goiter is a clinically or radiographically enlarged thyroid gland. It can be diffusely enlarged or nodular (either with a single nodule or multiple nodules, termed multinodular goiter). It can be toxic (with autonomous thyroid hyperfunction) or nontoxic (normal thyroid function). The most common cause of goiter worldwide is iodine deficiency. People living in inland mountainous regions where dietary supplementation is not practiced are at the highest risk for developing iodine deficiency. In the United States, more common etiologies of goiter include autoimmune thyroid disease (Hashimoto's thyroiditis or Graves' disease), simple nodular goiter, and thyroid carcinoma.

4. What are the clinical manifestations of a simple nodular goiter?

The clinical relevance of a simple (nonfunctioning) nodular goiter is related to its size and association with compressive symptoms. Both cervical and substernal goiters (those that extend through the thoracic outlet) can cause compression of nearby anatomic structures including the trachea, esophagus, or recurrent laryngeal nerves, leading to dyspnea, cough, dysphagia, globus sensation, and dysphonia. In addition, nodular goiters carry a similar risk of cancer as a single non-functioning nodule. Therefore multinodular goiters must be evaluated for malignancy using the same approach as for a single nodule.

5. What is the role of iodine in the formation of goiters?

Iodine is an essential dietary micronutrient and a key structural component of thyroxine (T_4) and triiodothyronine (T_3). Iodine deficiency leads to decreased production of thyroid hormones. This, in turn, leads to increased production of thyroid-stimulating hormone (TSH), which binds to

TSH receptors on thyroid follicular cells and causes an increase in the size of the thyroid gland, resulting in both diffuse and nodular growth.

6. What is the evaluation of a patient with compressive symptoms related to a goiter?

When a patient reports symptoms suggestive of compression from a thyroid nodule or goiter, further diagnostic studies may be warranted. Spirometry is noninvasive and provides an assessment of airflow during both inspiration and expiration, creating a flow volume loop curve. A goiter that causes fixed obstruction will show characteristic dampening of both inspiration and expiration curves. A barium swallow study (esophagram) can be used to evaluate for thyroid mass effect on the esophagus. Lastly, CT or MRI can be useful to evaluate the extent of a large goiter and assess for deviation or narrowing of the trachea or mass effect on the esophagus. Radioiodinated contrast materials should be used with caution due to the risk of iodine-induced thyrotoxicosis (Jod-Basedow effect).

7. What is Pemberton's sign?

Pemberton's sign, first described by Dr. Hugh Pemberton 1946, is useful for evaluating possible thoracic outlet obstruction by a substernal goiter. The patient is asked to elevate both arms overhead until they touch the sides of the face. Diffuse neck and facial congestion occur if the goiter obstructs the thoracic inlet by a "cork effect."

8. What is the initial approach to a patient with a newly discovered thyroid nodule?

The initial approach to a patient with a newly discovered thyroid nodule is also outlined in Fig. 43.1. The first step in the evaluation of a thyroid nodule(s) is to perform a focused history and physical examination. The history should note any factors that may increase the likelihood of thyroid cancer, including a history of head/neck ionizing radiation exposure (especially in childhood), a family history of thyroid cancer (or related condition if a syndromic cause is suspected), rapid growth of the nodule, or presence of compressive symptoms (dyspnea, cough, dysphagia, globus sensation, and dysphonia). The physical examination should include a complete neck exam including palpation of the thyroid gland and cervical lymph nodes. If substernal extension is suspected, an attempt to elicit Pemberton's sign should be made. Serum TSH should be measured. If serum TSH level is normal or elevated, an ultrasound of the thyroid gland and cervical lymph nodes should be performed to determine if a fine needle aspiration (FNA) biopsy is indicated. If serum TSH is low, serum free T_4 and total T_3 should be measured, and thyroid scintigraphy should be ordered to evaluate for an autonomously functioning thyroid nodule(s).

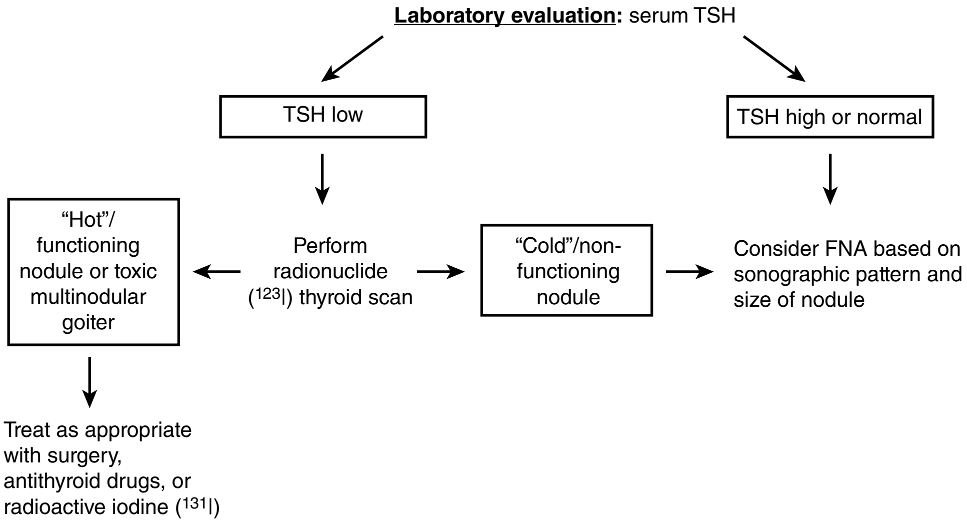
Laboratory evaluation: serum TSH
TSH low
TSH high or normal
"Hot"/ functioning nodule or toxic multinodular goiter
Perform radionuclide (^{123}I) thyroid scan
"Cold"/non-functioning nodule
Consider FNA based on sonographic pattern and size of nodule
Treat as appropriate with surgery, antithyroid drugs, or radioactive iodine (^{131}I)

Fig. 43.1 Algorithm for the evaluation of thyroid nodules. *FNA*, Fine-needle aspiration; *TSH*, thyroid stimulating hormone.

9. How does a nonfunctioning thyroid nodule differ from an autonomously functioning nodule?

One of the first steps in the initial evaluation of a thyroid nodule is to determine thyroid function by measuring serum TSH. If TSH is low, the next step is to measure serum free T_4 and total T_3 and to perform thyroid scintigraphy, preferably using radioiodine (usually I^{123}) as the radioisotope, but technetium-99m pertechnetate is another option. An autonomously functioning thyroid nodule is identified as a focal area of increased radiotracer uptake in association with decreased uptake in the remainder of the gland, indicating autonomous nodular function. A nonfunctioning nodule is one that demonstrates decreased radiotracer uptake. Such nodules should be considered for FNA. Indeterminate nodules are those that demonstrate similar uptake to the background thyroid and should be managed as nodules that are nonfunctioning. A toxic (autonomous) multinodular goiter will have mildly increased, heterogenous uptake. In general, autonomously functioning thyroid nodules do not require FNA for cytopathologic evaluation, as they are associated with a low likelihood of malignancy. However, FNA should be considered for functioning thyroid nodules that demonstrate highly suspicious findings on ultrasonography (e.g., extrathyroidal extension), as rare cases of autonomously functioning differentiated thyroid carcinoma may occur.

10. Why is Fine Needle Aspiration (FNA) performed under ultrasound (US) guidance?

The intention of thyroid nodule fine-needle aspiration (FNA) is to identify malignant thyroid nodules, and thereby select patients who require surgery. Thyroid nodule FNA should be performed with ultrasound guidance. Compared to FNA guided by palpation, ultrasound-guided FNA is associated with a lower rate of nondiagnostic cytology, a reduced false-negative rate, and higher cost effectiveness.

11. What is the approach to selecting thyroid nodules for FNA when multiple nodules are detected in a single gland?

When there is more than one nodule present in a single gland, each nodule should be evaluated for FNA independently according to its sonographic findings and size.

12. How is ultrasound used to risk stratify thyroid nodules and determine management?

Ultrasound should be used to determine a thyroid nodule's size in three dimensions, its location in the thyroid gland, and its appearance based on five grayscale ultrasound findings. These findings include (1) composition, which can be solid/predominantly solid, partially cystic, spongiform (>50% microcystic components) or entirely cystic; (2) echogenicity, which is determined relative to the normal thyroid parenchyma, and can be isoechoic (similar echogenicity), hyperechoic (more echogenic), hypoechoic (less echogenic), or markedly hypoechoic (as hypoechoic as the strap muscles); (3) shape in the transverse plane, which can be wider than tall (low risk) or taller than wide (suspicious); (4) margins, which can be regular or ill-defined (low risk) versus irregular, infiltrative, microlobulated, or spiculated (suspicious); (5) and the presence or absence of echogenic foci (macrocalcifications or punctate echogenic foci). Examples of thyroid nodule ultrasound images are shown in Fig. 43.2. All thyroid nodule risk stratification systems, including the American Thyroid Association's (ATA) pattern-based system and the American College of Radiology's Thyroid Imaging Reporting and Data System (ACR TI-RADS), use these same five grayscale characteristics to classify thyroid nodules into distinct risk of malignancy categories. Some systems also incorporate the appearance of a isoechoic/hyperechoic nodule's hypoechoic halo into risk stratification, where the halo represents either the compressed perinodular blood vessels or the fibrous capsule of an encapsulated nodule. The appearance of the halo can be classified as thin and regular (low risk) or thick and irregular (suspicious). Sonographic risk stratification systems also provide specific management recommendations according to the nodule's risk of malignancy, including when to perform FNA or follow up imaging. It should be noted that the presence of extrathyroidal extension (ETE) or abnormal cervical lymph nodes indicates a high likelihood of thyroid malignancy, and that traditional thyroid nodule FNA size cutoffs do not apply when such findings are documented.

13. Does every thyroid nodule have the same risk of cancer?

Certain constellations of ultrasound features predict the likelihood of thyroid cancer, in particular PTC. As previously described, ultrasound-based thyroid nodule risk stratification involves assessing a nodule's grayscale ultrasound features to determine its risk of malignancy. Features

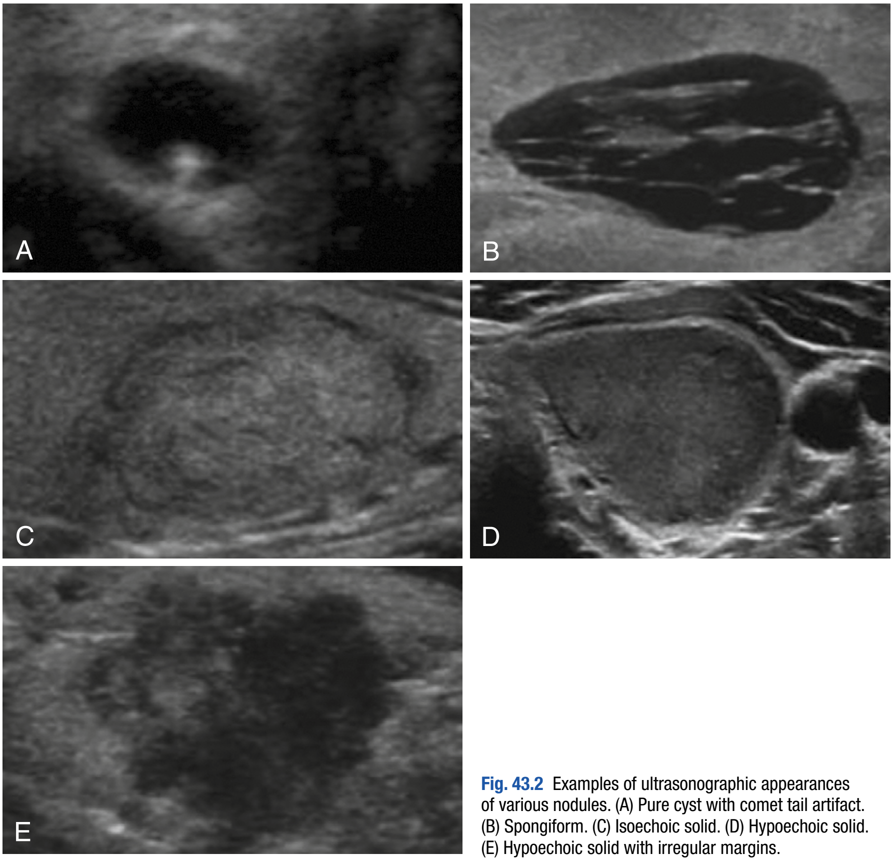

Fig. 43.2 Examples of ultrasonographic appearances of various nodules. (A) Pure cyst with comet tail artifact. (B) Spongiform. (C) Isoechoic solid. (D) Hypoechoic solid. (E) Hypoechoic solid with irregular margins.

associated with thyroid malignancy, especially PTC, include punctate echogenic foci (microcalcifications), hypoechogenicity, shape taller than wide, irregular margins, extrathyroidal extension, interrupted rim calcification with soft tissue extrusion, and presence of any abnormal appearing lymph nodes.

14. Which thyroid nodules need to be biopsied?

The decision to biopsy a thyroid nodule is based on the size and sonographic appearance of the nodule, which correspond to its risk of malignancy. The ATA, American Association of Clinical Endocrinologists, and ACR each have published recommendations describing when to consider FNA of a thyroid nodule. These criteria are summarized in Table 43.1. However, it is anticipated that the ATA will release their updated sonographic pattern system and new FNA thresholds in 2025.

15. How is thyroid cytology interpreted?

After thyroid nodule FNA is performed, the aspiration material is prepared for cytology by either conventional smear methods or liquid-based preparation, which helps reduce variation and artifact. Cytopathology findings are reported using the Bethesda System for Reporting Thyroid Cytopathology, which was initially proposed in 2007 and most recently updated in 2023. Based on certain features, an FNA sample is classified into one of six categories: (1) nondiagnostic; (2) benign; (3) atypia of undetermined significance (AUS); (4) follicular neoplasm (FN); (5) suspicious for malignancy (SFM); and (6) malignant. Each category is associated with a corresponding risk of malignancy/NIFTP and recommendations for management. Rapid on-site evaluation (ROSE) of

TABLE 43.1 Comparison of Guidelines for Thyroid FNA

ATA	AACE/ACE-AME	ACR
High Suspicion Hypoechoic + one of the following: Taller than wide, microcalcifications, irregular margins, extrathyroidal extension, interrupted rim calcification with soft tissue extrusion, suspicious lymph nodes **Biopsy when ≥1 cm**	High Risk At least one of the following: Marked hypoechogenicity, spiculated or microlobulated margins, microcalcifications, taller than wide, extrathyroidal growth, pathologic adenopathy **Biopsy when ≥1 cm** **Consider biopsy when 5–10 mm**	Highly Suspicious ≥7 points based on composition, echogenicity, shape, margins, and echogenic foci **Biopsy when ≥1 cm**
Intermediate Suspicion Hypoechoic (without features described above) **Biopsy when ≥1.5 cm**	Intermediate Risk Slightly hypoechoic or isoechoic with ovoid-to-round shape and smooth or ill-defined margins, intranodular vascularization, elevated stiffness at elastography, macro- or continuous rim calcifications, hyperechoic spots of uncertain significance **Biopsy when ≥2 cm**	Moderately Suspicious 4–6 points based on composition, echogenicity, shape, margins, and echogenic foci **Biopsy when ≥1.5 cm**
Low Suspicion Hyperechoic, isoechoic, partially cystic with eccentric solid area (without features described above) **Biopsy when ≥1.5 cm**	Low Risk Cysts (>80%), mostly cystic (>50%) with reverberating artifacts (without suspicious ultrasonographic signs), isoechoic spongiform **Biopsy when ≥2 cm only when increasing in size or in special circumstances**	Mildly Suspicious 3 points based on composition, echogenicity, shape, margins, and echogenic foci **Biopsy when ≥2.5 cm**
Very Low Suspicion Spongiform, partially cystic (without features described above) **Biopsy when ≥2.0 cm**[a]		Not Suspicious 2 points based on composition, echogenicity, shape, margins, and echogenic foci **Biopsy not recommended**
Benign Pure cyst **Biopsy not recommended**		Benign 0 points based on composition, echogenicity, shape, margins, and echogenic foci **Biopsy not recommended**

[a] Can consider clinical and ultrasonographic follow-up in lieu of FNA biopsy.

AACE/ACE/AME, American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi; *ACR,* American College of Radiology; *ATA,* American Thyroid Association; *FNA,* fine-needle aspiration.

cytology specimens by cytotechnologists or pathologists can help lower the nondiagnostic rate by ensuring FNA samples are adequate—at least 6 groups of 10 or more follicular cells that are well visualized. ROSE is more easily accomplished using FNA smears than liquid-based preparations.

16. What is the management of a thyroid nodule that is found to have benign cytology on FNA?

The overall risk of malignancy for thyroid nodules with benign cytology is approximately 1–2%. The estimated risk of malignancy reported by the 2023 Bethesda system is higher (2–7%) because this data was extracted from surgical series, leading to a potential overestimation of risk. Given the low risk for malignancy after an initial benign FNA, no immediate follow-up testing is warranted. It is recommended that all thyroid nodules be followed clinically (by history and physical examination). If FNA is performed, thyroid nodules in keeping with the ATA very low suspicion ultrasound pattern do not require US follow up for malignancy assessment thereafter if benign. Neck US should be repeated during follow-up for most other thyroid nodules, where the initial follow-up interval is determined by the baseline sonographic appearance of the nodule. Nodules that develop new suspicious sonographic features during follow-up should undergo repeat FNA. Growth has not been shown to be a reliable predictor of missed malignancy and should not be considered a strong indication for repeat FNA. Nodules that are classified as ATA high-suspicion sonographic pattern (generally comparable to TI-RADS 5 using the ACR system) retain a high probability of malignancy after a single benign FNA, and thus should undergo repeat neck US and FNA within 12 months. If a nodule has undergone two benign FNA biopsies, neither continued US follow-up nor repeat FNA is warranted.

17. What is the management of an indeterminate thyroid nodule?

Indeterminate thyroid nodules are nodules that are not definitively benign or malignant and include AUS (Bethesda III), FN (Bethesda IV), and SFM (Bethesda V) cytology. The estimated risk of malignancy (including NIFTP) for AUS, FN, and SFM cytology is 13–30%, 23–34%, and 67–83%, respectively. With AUS cytology, the sonographic pattern and patient risk factors and preferences are taken into consideration to determine the need for surgery versus repeat FNA or clinical and ultrasound surveillance. Molecular diagnostic testing may be used adjunctively to help inform clinical decision-making. With FN cytology, either diagnostic surgery (lobectomy) or molecular testing is appropriate. The management of nodules with SFM cytology is the same as for malignant nodules (Bethesda VI).

18. What is the role of molecular testing in thyroid nodule management?

The ATA guidelines recommend that molecular diagnostic testing be considered to help inform the management of thyroid nodules with indeterminate cytology (specifically AUS and FN). The commercially available molecular diagnostic tests include DNA-based and RNA-based next-generation sequencing to detect the presence of genetic alterations, including point mutations, insertions or deletions, gene fusions, chromosomal copy number alterations, and changes in gene expression. These tests have demonstrated high sensitivity (91–98%) and reasonably high specificity (68–86%). While molecular testing was initially used to provide an auxiliary risk assessment for malignancy and reduce the need for unnecessary surgical interventions, its use has expanded to help guide prognosis and management for thyroid cancer.

19. What is the management of a thyroid nodule that is found to be malignant after FNA?

Malignant (Bethesda VI) cytology is associated with a 97–100% risk of malignancy/NIFTP. Surgical resection (total thyroidectomy or lobectomy) is the recommended management approach for most thyroid nodules with malignant cytology, although active surveillance may be an option for PTCs that are smaller than 1–1.5 cm.

20. What is the management of a thyroid nodule that does not meet criteria for FNA?

The follow-up of a thyroid nodule that does not initially meet criteria for FNA depends on its pretest probability of malignancy, which is based on its initial sonographic appearance. Cysts and spongiform nodules do not require routine imaging follow up for malignancy assessment.

KEY POINTS

- Thyroid nodules are common, but only a small percentage of nodules are malignant.
- The initial evaluation of a thyroid nodule involves measurement of serum TSH and ultrasound of the thyroid gland and cervical nodes. A subnormal TSH should prompt diagnostic radionucleotide (I^{123}) scanning.
- The decision to biopsy a thyroid nodule depends on its size and sonographic features.
- Molecular testing can be useful in the management of thyroid nodules with indeterminate cytology, specifically for AUS and FN cytology.

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CHAPTER 44

Thyroid Cancer

Amanda La Greca

INTRODUCTION

1. How common is thyroid cancer?

In the United States, thyroid cancer is the 12th most common cancer, with an estimated lifetime prevalence of 1.2%. It is the fifth most common cancer in women and the most common cancer among women 20–34 years old. The median age at diagnosis is 51 years old, and it is diagnosed two to four times more frequently in women than in men. The incidence of thyroid cancer has been rising by about 3% per year, largely due to identification of incidental thyroid nodules on screening or on imaging performed for other reasons. Almost the entire increase was attributable to small papillary thyroid cancer. The rate of death from thyroid cancer has been stable at 0.4%, suggesting that the increased incidence is primarily the result of diagnosis of subclinical, indolent tumors.

2. What are the types of thyroid cancer?

The most common type of thyroid cancer is differentiated thyroid cancer (DTC), which comprises >90% of all thyroid cancers and includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), oncocytic thyroid carcinoma (OTC), differentiated high-grade thyroid carcinoma (DHGTC), and poorly differentiated thyroid carcinoma (PDTCA). Other types of thyroid cancer include medullary and anaplastic thyroid cancers. Rarely, other tumor types including lymphoma, salivary gland tumors, and metastases from nonthyroid malignancies (e.g., breast, renal cell) can be seen in the thyroid gland.

3. How does thyroid cancer present?

Thyroid cancer is often identified when people present with a palpable thyroid nodule. Thyroid nodules may also be identified on imaging performed for evaluation of other thyroid disorders or incidentally on imaging performed for unrelated reasons. Diagnostic workup typically includes measurement of serum TSH, neck ultrasound and, if indicated, fine-needle aspiration biopsy (see Chapter 43).

DIFFERENTIATED THYROID CANCER

4. What is differentiated thyroid cancer?

DTC arises from thyroid follicular epithelial cells. PTC is the most common type of DTC and is associated with nuclear changes (e.g., pseudoinclusions, nuclear grooves) on pathology. Several PTC subtypes can be seen, the most common of which are the classic and follicular variants. Some PTC subtypes demonstrate more aggressive clinical behavior (e.g., tall cell and hobnail variants). The encapsulated follicular variant of PTC, when lacking invasion, necrosis, or high mitotic activity, has been renamed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and is no longer considered a malignancy. FTC, the second-most common DTC, is distinguished from a benign follicular adenoma by the presence of capsular and/or vascular invasion. Oncocytic thyroid carcinoma (OTC), previously known as Hurthle cell carcinoma and considered as a subtype of FTC, has been reclassified by the 2017 WHO Classification as a separate entity, given its unique biological and clinical features and different genetic profile from FTC. PDTC is thought to devolve from well-differentiated thyroid cancer; it is associated with more aggressive behavior and a poorer prognosis. The 5th edition of the WHO Classification of Thyroid Tumors (2022) also introduced a new category of high-grade follicular cell derived, nonanaplastic carcinoma that includes poorly differentiated thyroid carcinoma (PDTCA) and differentiated high-grade thyroid carcinoma (DHGTC). In both cases, clinical behavior is considered intermediate between well-differentiated and anaplastic carcinoma.

5. What are risk factors for differentiated thyroid cancer?

Thyroid cancer is more common in women than men. Most DTC arises sporadically; however, approximately 5–10% may have a familial association, although the genetic drivers of this association are not well understood. Several genetic syndromes are also associated with DTC, including PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome (also known as Cowden's disease), familial adenomatous polyposis, Carney complex, and Werner syndrome or progeria. A history of ionizing radiation exposure (>10 rads), including childhood head and neck irradiation or environmental radiation exposure, increases the risk of thyroid cancer.

6. What staging is used for differentiated thyroid cancer?

Ten-year disease-specific survival (DSS) is based on stage at diagnosis according to the American Joint Committee on Cancer Staging 8th edition system (see Table 44.1). Of note, age is one of the factors used to determine stage in DTC. For patients <55 years of age, the highest stage is II, which indicates the presence of distant metastases. For patients age 55 years and older, the stages are I–IV. Estimated 10-year DSS is ≥98% for stage I, 85–95% for stage II, 60–70% for stage III, and <50% for stage IV.

7. What is the preoperative evaluation of patients with DTC?

All patients undergoing lobectomy or total thyroidectomy should receive a preoperative neck ultrasound to carefully evaluate cervical lymph nodes in the central and lateral neck compartments as well as for gross extrathyroidal extension. Sonographically suspicious cervical lymph nodes greater than 8 to 10 mm in the greatest diameter should be biopsied prior to surgery if this would change surgical planning (Fig. 44.1). CT or MRI of the neck can be considered if invasive (gross extrathyroidal extension, bulky adenopathy, or disease concerning for thoracic involvement) is suspected. It is also recommended that serum calcium be measured prior to thyroid surgery to rule out concomitant primary hyperparathyroidism, another common endocrine disorder that can be addressed at the time of thyroid surgery (see Chapter 19). Laboratory assessment of serum thyroglobulin (Tg) and antithyroglobulin antibodies (TgAb) prior to surgery may allow TgAb positivity, causing negative interference with serum Tg measurement in immunometric assays, to be identified. Although Tg is a sensitive tumor marker following thyroidectomy, absolute serum Tg levels prior to surgery do not correlate with prognosis since normal thyroid tissue also produces Tg (see Question 13).

8. What type of surgery should patients with DTC undergo?

Surgery is the mainstay of DTC treatment. The exception is papillary thyroid microcarcinoma (tumors ≤1 cm) without evidence of extrathyroidal extension, lymph node involvement, or distant metastases, for which active surveillance may also be an appropriate option. Most evidence supports that either hemithyroidectomy (lobectomy) or total thyroidectomy yields equivalent outcomes for tumors ≤4 cm without evidence of extrathyroidal extension, nodal involvement, or distant metastases. For patients with thyroid cancers greater than 4 cm, cancer of any size with gross extra thyroidal extension, or clinically apparent metastatic disease to lymph nodes, the initial surgical procedure should include total thyroidectomy with gross removal of all primary tumor and node dissection. Therapeutic central and/or lateral neck dissections should be performed for clinically or histologically confirmed lymph node involvement in the relevant compartment. Prophylactic central neck dissections are also performed when there is lateral nodal involvement or suspected extrathyroidal extension. See also the chapter on thyroid surgery.

9. What is the role of levothyroxine administration in the treatment of DTC?

Following thyroidectomy, thyroid hormone administration (oral levothyroxine) is required due to loss of endogenous thyroid hormone production. Under normal physiologic conditions, binding of thyroid-stimulating hormone (TSH) to TSH receptors on thyroid follicular cells mediates growth. Because DTC cells usually express the TSH receptor, supraphysiologic levothyroxine doses may be administered to suppress serum TSH, thereby preventing TSH-mediated

TABLE 44.1 Differentiated Thyroid Cancer Staging System—AJCC 8th Edition

Primary Tumor (T)	
T CATEGORY	**DEFINITION**
TX	Cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤1 cm, limited to thyroid
T1b	Tumor >1 cm but ≤2 cm, limited to thyroid
T2	Tumor >2 cm but ≤4 cm, limited to thyroid
T3a	Tumor >4 cm, limited to thyroid
T3b	Gross extrathyroidal extension to strap muscles
T4a	Gross extrathyroidal extension to subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Gross extrathyroidal extension to prevertebral fascia, carotid artery, or mediastinal vessels
Regional Lymph Node (N)	
N CATEGORY	**DEFINITION**
NX	Cannot be assessed
N0a	Cytology- or histology-confirmed benign lymph nodes
N0b	No clinical or radiologic evidence of lymph node metastases
N1a	Central (level VI or VII) lymph node metastases
N1b	Lateral (level I–V) or retropharyngeal lymph node metastases
Distant Metastasis (M)	
M CATEGORY	**DEFINITION**
M0	No distant metastases
M1	Distant metastases present
Staging	
STAGE	**CRITERIA**
I	Age <55: Any T, Any N, M0 Age ≥55: T1–2, N0, M0
II	Age <55: Any T, Any N, M1 Age ≥55: T1–2, N1, M0 T3, Any N, M0
III	Age ≥55: T4a, Any N, M0
IVA	Age ≥55: T4b, Any N, M0
IVB	Age ≥55: Any T, Any N, M1

stimulation of thyroid cancer cell growth and potentially reducing the risk of thyroid cancer recurrence. In general, low-risk patients with an excellent response to therapy have a goal TSH of 0.5–2.0 mU/L, high-risk patients or those with structural incomplete responses have a goal TSH of <0.1 mU/L, and patients with indeterminate or biochemical incomplete response to therapy have a goal TSH of 0.1–0.5 mU/L. Less strict TSH goals may later be targeted in patients with a sustained excellent response to therapy. In all patients, the potential cancer benefit must be weighed against the risks of subclinical hyperthyroidism, especially bone loss and risk of arrhythmia in older patients.

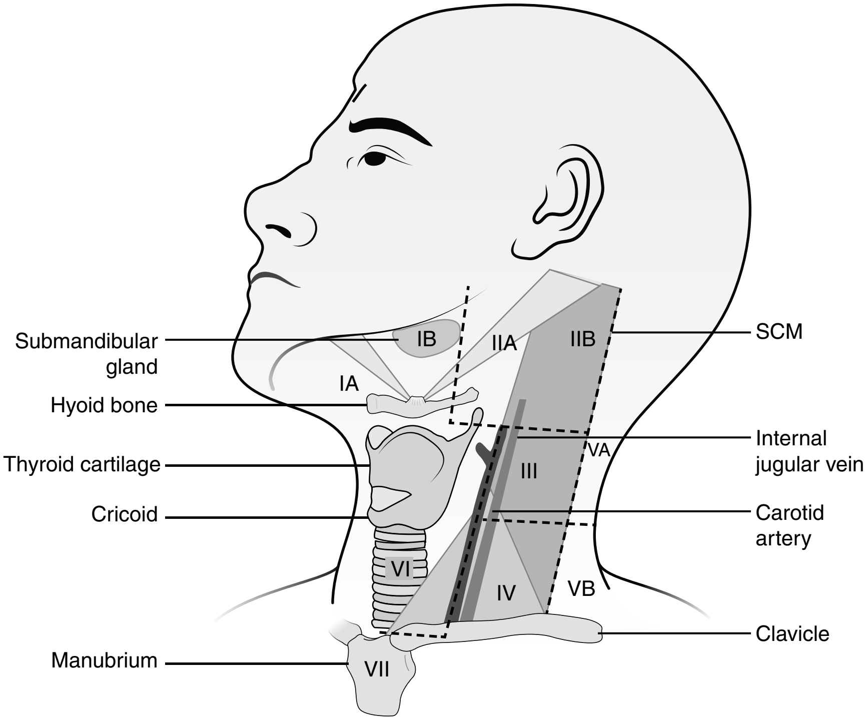

Fig. 44.1 Cervical lymph node zones. From Medina JE. Metastases to the neck. In: Flint PW, Haughey BH, Lund VJ, et al., eds. *Cummings Otolaryngology: Head and Neck Surgery*. 6th ed. Elsevier; 2015:1836.

TABLE 44.2 RAI Approaches

RAI STRATEGY	TARGET	PURPOSE	DOSE
Remnant ablation	Remaining normal thyroid tissue	Facilitate posttreatment follow-up	30 mCi
Adjuvant therapy	Suspected but undocumented residual disease	Reduce risk of recurrence	Up to 150 mCi
Therapy	Persistent/metastatic disease	Improve survival	100–200 mCi (consider reduced dose in elderly or dosimetry)

10. When should radioactive iodine be offered to patients with differentiated thyroid cancer?

As DTC usually expresses the sodium-iodide symporter, radioactive iodine (RAI; ^{131}I) administered postoperatively may be taken up by and destroy thyroid cancer cells as well as any residual normal thyroid tissue. General RAI treatment approaches are outlined in Table 44.2. However, these indications must be balanced against the potential risks of RAI, including sialadenitis, dental caries, nasolacrimal duct obstruction, and increased relative risk of secondary malignancies (e.g., leukemia). In general, RAI is not indicated for low-risk thyroid cancer, can be considered in intermediate-risk patients and should be given to high-risk patients. When RAI is administered, a posttherapy whole-body scan should be completed to document sites of RAI-avid disease.

TABLE 44.3 Response to Therapy

CATEGORY	FEATURES
Excellent	• Negative imaging, and • Suppressed Tg < 0.2 ng/mL or stimulated Tg ≤ 1 ng/mL
Indeterminate	• Suppressed or stimulated Tg not meeting definition for another category, or • Stable or declining TgAb levels, or • Nonspecific findings on imaging
Biochemical incomplete	• Negative imaging, and • Suppressed Tg ≥ 1 ng/mL, stimulated Tg > 10 ng/mL, or rising TgAb
Structural incomplete	• Imaging suggestive of or biopsy-proven residual or recurrent disease

Tg, thyroglobulin; *TgAb*, antithyroglobulin antibody.

11. How is radioactive iodine given?

In order to increase the uptake of RAI into cells, patients are placed on a low-iodine diet for 1–2 weeks prior to treatment and TSH is deliberately made elevated. The latter has traditionally been accomplished by stopping thyroid hormone therapy (thyroid hormone withdrawal) 3–4 weeks before RAI. In patients with DTC in whom RAI remnant ablation or adjuvant therapy is planned, preparation with recombinant human thyrotropin (rhTSH) stimulation is preferred over thyroid hormone withdrawal. In patients with known distant metastases, either LT4 withdrawal or rhTSH can be used for preparation (ATA, 2024). Patients should be counseled about isolation precautions following RAI administration to minimize potential radiation exposure to other people and animals. Women of reproductive age should have a serum pregnancy test prior to RAI and be advised to avoid pregnancy for at least 6-months following RAI treatment due to the associated risk of ablation of the fetal thyroid and the recommendation to have stable thyroid function prior to pregnancy.

12. In addition to clinical staging, how is prognosis assessed in patients with differentiated thyroid cancer?

The American Thyroid Association (ATA) guidelines for the management of DTC recommend classifying patients as having low, intermediate, or high risk of thyroid cancer recurrence based on the clinical, pathologic, and radiologic findings at the time of initial diagnosis and treatment. High-risk features include distant metastases, gross extrathyroidal extension or residual tumor, FTC with extensive vascular invasion (>4 foci), extranodal extension, or lymph node metastases >3 cm in size. Risk of recurrence is intermediate in the setting of aggressive PTC subtypes, PTC with vascular invasion, clinically apparent adenopathy, >5 involved lymph nodes, or persistent RAI-avid metastatic foci in the neck after initial RAI administration. Risk of recurrence is low for patients lacking these features. Prognosis is reevaluated at every visit by designating a patient's response to therapy as excellent, biochemically incomplete, structurally incomplete, or indeterminate based on the results of serum Tg testing and imaging (see Table 44.3).

13. How should patients with DTC be followed to detect recurrence?

Patients with DTC should be followed with physical examination, Tg and TgAb measurements, and neck ultrasound imaging. The frequency of follow-up is dictated by the patient's risk of recurrence and response to therapy. Tg is a protein precursor to thyroid hormone made by intact thyroid tissue but is also made by most DTCs. Serum Tg can be used as a DTC tumor marker in patients who have undergone thyroidectomy. TgAb are present in up to 30% of DTC patients, however, and interfere with standard immunometric Tg measurements, causing falsely low serum Tg levels. In patients with any level of detectable TgAb, nonimmunometric methods of Tg measurement such as radioimmunoassay or liquid chromatography – tandem mass spectrometry should be considered. As the most common site of PTC recurrence is in cervical lymph nodes, combining Tg/TgAb measurement with neck ultrasound detects recurrences in most patients. In patients with rising Tg but no evidence of disease on neck ultrasound, additional imaging (chest, abdomen, bone, brain) may be required to identify sites of disease.

14. Define radioiodine-refractory thyroid cancer.

RAI-refractory thyroid cancer is considered to be present if it meets any of the following conditions: malignant tissue that never concentrates RAI, malignant tissue that loses the ability to concentrate RAI, only some of the tissue concentrates RAI, and malignant tissue grows despite concentrating RAI.

15. What treatment modalities are used for recurrent and/or metastatic differentiated thyroid cancer?

In general, treatment modalities for recurrent and/or metastatic DTC fall into four categories: close observation, directed therapies, systemic therapies, and, where applicable, clinical trials. In a patient with low-volume, slowly progressive disease, close observation with TSH suppression and regular clinical, laboratory and radiologic surveillance may be reasonable. Directed therapies, such as surgery, external beam radiotherapy (EBRT), ethanol, or radiofrequency ablationof lymph node metastases, may be considered for localized disease. RAI can be used even in the metastatic setting for disease that retains the ability to concentrate and respond to iodine, but not in patients with RAI-refractory disease. For patients with RAI-refractory DTC with high-volume, progressive, or symptomatic disease, genomic tumor testing to identify actionable oncogenic driver alterations should be performed prior to initiating systemic therapy. For patients with progressive RAI-refractory DTC without an actionable mutation and FDA-approved first-line therapy, multikinase inihibitor (MKI) therapy with either lenvatinib or sorafenib is recommended. In most cases, lenvatinib is the preferred first-line MKI. In patients with progressive RAI-refractory DTC harboring an oncogenic BRAF V600E mutation, BRAF V600E-directed therapy may be considered as first line for patients who are poor candidates for lenvatinib. In patients with progressive RAI-refractory DTC harboring an oncogenic *NTRK*, *RET*, or *ALK* fusion, gene-specific therapy is recommended as first line (ATA, 2024). Adverse events are common with these agents, so the risks of untreated progressive disease must be weighed against the risks of therapy. Gene-specific therapy is in general better tolerated, but none of these therapies are curative, and resistance is nearly universal. Denosumab or bisphosphonates should be added in patients with bone metastases to reduce the frequency of adverse skeletal events.

KEY POINTS: DIFFERENTIATED THYROID CANCER

1. Differentiated thyroid cancer (DTC) is the most common type of thyroid cancer and includes papillary, follicular, oncocytic, differentiated high-grade, and poorly differentiated thyroid carcinoma.
2. Prognosis in DTC is determined by initial staging, risk stratification, and ongoing assessment of response to therapy.
3. The main modalities of treatment of DTC are surgery and TSH suppression, with or without radioactive iodine therapy.
4. For patients with progressive RAI-refractory DTC, systemic therapy can be started with multikinase inihibitor therapy or gene specific therapy.

ANAPLASTIC THYROID CANCER

16. What is anaplastic thyroid cancer?

Anaplastic thyroid cancer (ATC) comprises approximately 1–2% of all thyroid cancers but carries the worst prognosis with a median survival of 3–6 months. In contrast to DTC, patients are usually older at diagnosis and frequently present with a rapidly enlarging neck mass and compressive symptoms. Although derived from thyroid follicular cells, ATC cells are dedifferentiated and no longer express the TSH receptor or sodium-iodide symporter; TSH suppression and RAI therapy are therefore not components of ATC management. On pathology, high degrees of necrosis and mitotic activity are frequently seen and traditional markers of thyroid tissue are typically absent

TABLE 44.4 Anaplastic Thyroid Cancer Staging System

STAGE	CRITERIA
IVA	T1-T3a, N0, M0
IVB	T1-T3a, N1, M0 T3b-T4, Any N, M0
IVC	Any T, Any N, M1

on immunostaining. ATC is frequently found in conjunction with or in patients with a history of DTC and is generally thought to devolve from DTC as more mutations, such as P53, are acquired.

17. How is anaplastic thyroid cancer staged?

Definitions of primary tumor, regional lymph node involvement, and distant metastases are the same as in DTC (see Table 44.1). However, all ATC is considered stage IV disease, as depicted in Table 44.4. Unlike DTC, age is not a component of the staging system. Expedited imaging with neck ultrasound, cross-sectional imaging of the neck and chest, and possibly ^{18}FDG-PET scan should be performed as part of the initial staging workup. Early molecular testing should also be performed because the presence of a BRAF-V600E mutation could direct the choice of systemic therapy.

18. How is anaplastic thyroid cancer treated?

ATC should be managed under the care of a multidisciplinary team. If disease is considered resectable (e.g., stage IVA and some IVB), surgery (total thyroidectomy with therapeutic central and lateral neck dissection) should be undertaken on an urgent basis. In general, multimodal therapy involving surgery, radiation, and systemic therapy is the optimal approach in the management if these aggressive tumors. Patients with unresectable locoregional disease (unresectable stage IVB) may receive neoadjuvant EBRT and systemic therapy, which includes multikinase inhibitors, cytotoxic agents, and immunotherapy. If disease becomes resectable after neoadjuvant therapy, surgery may be reconsidered. Treatment of metastatic ATC (stage IVC) is generally palliative but may include EBRT (especially for symptomatic lesions) and/or systemic therapy. Dabrafenib and trametinib are tyrosine kinase inhibitors that specifically target the BRAF-V600E mutation and are approved for the use in ATC patients whose tumors harbor this mutation. Several different cytotoxic chemotherapy regimens have been described, usually involving doxorubicin, platinum-based agents, and/or taxanes, but all have limited efficacy.

KEY POINTS

1. Anaplastic thyroid cancer (ATC) is a rare, aggressive, undifferentiated form of thyroid cancer, with an extremely poor prognosis.
2. The optimal therapeutic approach should be multimodal, including surgery (if able to achieve complete resection), radiation and systemic therapy, including multikinase inhibitors, cytotoxic agents, and immunotherapy depending on mutational status.

MEDULLARY THYROID CANCER

19. What is medullary thyroid cancer?

Unlike DTC and ATC, medullary thyroid cancer (MTC) arises from parafollicular C-cells within the thyroid gland. As these C cells develop embryologically from neural crest cells, MTC is considered a neuroendocrine tumor. C cells produce calcitonin, which can thus be used to identify MTC histologically with immunostains and biochemically as a serum tumor marker to follow disease. Since MTC is not derived from thyroid follicular cells, it does not respond to TSH suppression or RAI therapy. MTC, especially when there is a high tumor burden, can sometimes be associated with watery diarrhea.

20. What genetic syndromes are associated with medullary thyroid cancer?

While the majority of MTC is sporadic, about 25% of cases are hereditary. MTC can occur as a component of multiple endocrine neoplasia type 2A (MEN2A) or type 2B (MEN2B) (see Chapter 60). MEN2A, by far more common, is comprised of several clinical subtypes and may be associated with pheochromocytoma and/or primary hyperparathyroidism. MEN2B is frequently associated with pheochromocytoma (but not hyperparathyroidism) and a characteristic physical appearance (marfanoid habitus and mucosal neuromas). Both MEN2A and MEN2B, as well as about 50% of sporadic MTC, are associated with mutations in the *RET* oncogene, and different mutations are associated with specific phenotypes. The *RET* codon M918T mutation is the most common mutation in MEN2B; the aggressive disease in patients with this mutation tends to present in infancy. Genetic screening of first-degree relatives is recommended for all patients with MTC. Children known to carry high-risk RET mutations should have a prophylactic thyroidectomy.

21. How is medullary thyroid cancer staging determined?

The AJCC staging system for MTC uses the same definitions for primary tumor, regional lymph nodes, and distant metastases as for DTC (see Table 44.1). MTC staging is outlined in Table 44.5. Regional lymph node and distant metastases are common in MTC, present in up to 80% and 10% of patients, respectively.

22. What preoperative evaluation is indicated?

After confirmation of the diagnosis of MTC (usually based on fine-needle aspiration biopsy of a thyroid nodule), patients should have a neck ultrasound to evaluate for suspicious lymph nodes. Preoperative serum calcitonin and carcinoembryonic antigen (CEA) levels should also be measured. If serum calcitonin is >500 pg/mL or if there is suspicion for invasive local disease, cross-sectional imaging of the neck and chest, dedicated three-phase CT or MRI of the liver, and/or skeletal imaging can be performed. Additionally, patients with suspected hereditary MTC should be evaluated for pheochromocytoma and hyperparathyroidism prior to surgery. Rarely, MTC can secrete adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone, causing ectopic Cushing's syndrome (see Chapter 28).

23. What is the recommended extent of surgery for medullary thyroid cancer?

Total thyroidectomy with central neck dissection is the primary treatment for MTC. Lateral neck dissection should be performed if there is sonographic evidence of lymph node metastases. As preoperative serum calcitonin and CEA levels are associated with disease extent, some advocate for ipsilateral lateral neck dissection when calcitonin is >20 pg/mL and contralateral lateral neck dissection when calcitonin is >200 pg/mL. If distant metastases are present, the initial surgery should be less aggressive (e.g., total thyroidectomy alone) in order to minimize morbidity. Adjuvant EBRT may be considered in patients at high risk of locoregional recurrence. Postoperatively, patients should be started on replacement doses (approximately 1.6 mcg/kg) of levothyroxine, targeting a normal serum TSH level. Also see the chapter on thyroid surgery.

TABLE 44.5 Medullary Thyroid Cancer Staging System

STAGE	CRITERIA
I	T1, N0, M0
II	T2–3, N0, M0
III	T1–3, N1a, M0
IVA	T1–3, N1b, M0 T4a, Any N, M0
IVB	T4b, Any N, M0
IVC	Any T, Any N, M1

24. How should patients with medullary thyroid cancer be followed after surgery?

All patients should have a physical examination, neck ultrasound, and serum calcitonin and CEA measurements 6 months after surgery. Low or undetectable calcitonin levels are associated with an excellent prognosis. Postoperative calcitonin levels up to 150 pg/mL are associated with cervical lymph node metastases; levels >150 pg/mL may be associated with distant metastases and should prompt further imaging to identify sites of metastasis. Calcitonin and CEA doubling times should be calculated during follow-up. Doubling times of <6 months are associated with a poor prognosis, while doubling times of >2 years are associated with a good prognosis. Tools for calculating the calcitonin and CEA doubling times can be accessed on the ATA website (www.thyroid.org).

25. How is metastatic medullary thyroid cancer treated?

Therapy for metastatic MTC may be directed or systemic. Examples of directed therapy include EBRT for bone or brain metastases, and surgery or chemoembolization for limited liver metastases. Bisphosphonates or denosumab should be added for bone metastases. As in DTC, systemic treatment of MTC involves multikinase inhibitors and gene-specific therapy. There are two FDA-approved multikinase inhibitors in this setting: vandetanib and cabozantinib. Recently, a third drug was approved by the FDA for the treatment of RET-mutated MTC in adults and children: selpercatinib. Adverse events are common with the multikinase inhibitors and much less with gene-specific therapy (RET-inhibitor). Additionally, metastatic MTC is frequently associated with diarrhea, which is usually managed with antimotility drugs such as loperamide.

KEY POINTS

- Medullary thyroid cancer (MTC) is a neuroendocrine tumor arising from parafollicular C-cells within the thyroid gland.
- MTC may be associated with multiple endocrine neoplasia types 2A and 2B.
- Surgery is the mainstay of treatment; systemic therapies for those with metastatic disease include the multikinase inhibitors vandetanib and cabozantinib and gene-specific therapy with Selpercatinib for RET-mutated MTC.

WEBSITES

American Thyroid Association: www.thyroid.org

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CHAPTER 45

Thyroid Emergencies

Michael T. McDermott

1. What is thyroid storm or thyroid crisis?

Thyroid storm or crisis is a life-threatening condition characterized by an exaggeration of the manifestations of thyrotoxicosis; some prefer the term “decompensated thyrotoxicosis.” When thyroid storm was first described, the acute mortality rate was nearly 100%. Today the prognosis is significantly improved if appropriate therapy is initiated early, with recent mortality rates of <10% being reported.

2. How do patients develop thyroid storm?

Thyroid storm usually occurs in patients who have unrecognized or inadequately treated thyrotoxicosis and a superimposed precipitating event such as thyroid surgery, nonthyroid surgery, infection, or trauma.

3. What are the clinical manifestations of thyroid storm?

Fever (>102°F) is the cardinal manifestation. Tachycardia is usually present, and tachypnea is common, but the blood pressure is variable. Cardiac arrhythmias, congestive heart failure, and ischemic heart symptoms may develop. Nausea, vomiting, diarrhea, and abdominal pain are frequent features (Fig. 45.1). Central nervous system manifestations include hyperkinesis, psychosis, and coma. A goiter is a helpful finding but is not always present.

4. What laboratory abnormalities suggest thyroid storm?

Serum thyroxine (total T_4 and free T_4) and triiodothyronine (total T_3 and free T_3) are usually significantly elevated and serum thyroid-stimulating hormone (TSH) is undetectable. However, these tests cannot reliably distinguish thyroid storm from uncomplicated thyrotoxicosis. Other common findings include anemia, leukocytosis, hyperglycemia, azotemia, hypercalcemia, and elevated liver enzymes.

5. How is the diagnosis of thyroid storm made?

Thyroid storm is diagnosed based on suspicious but nonspecific clinical findings supported by laboratory testing. Table 45.1 provides a useful published and validated scoring system to aid in diagnosis (Burch HB). A different scoring system has been proposed by a separate group (Akamizu T). Although scoring systems are helpful, they are no substitute for a careful evaluation and sound clinical judgment by an experienced clinician.

6. What other conditions may mimic thyroid storm?

Sepsis, pheochromocytoma, and malignant hyperthermia may have similar presentations.

7. How should patients with thyroid storm be treated?

The immediate goals are to decrease thyroid hormone synthesis, inhibit thyroid hormone release, reduce the heart rate, support the circulation, and treat the precipitating conditions. Because beta_1-adrenergic receptors are significantly increased in this condition, beta_1-selective blockers are the preferred agents for heart rate control. Table 45.2 lists the medications and doses commonly used to treat thyroid storm.

8. When traditional therapy fails, what additional options should be considered?

Plasma exchange or plasmapheresis can be lifesaving measures in thyroid storm patients who have not adequately responded to the above standard measures.

9. Define myxedema coma

Myxedema coma is a life-threatening condition characterized by an exaggeration of the manifestations of hypothyroidism; some prefer the term “decompensated hypothyroidism.” Myxedema coma originally had a mortality rate of 100%. Today the outlook is much improved for appropriately treated patients; mortality rates in recent studies have varied from 0% to 45%.

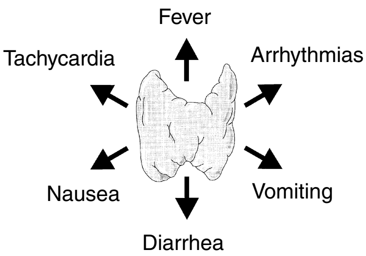

Fig. 45.1 Features of thyroid storm.

TABLE 45.1 Thyroid Storm Scoring System

Temperature	
FEVER (°F)	**SCORE**
99–99.9	5
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
≥104	30
Central Nervous System	
AGITATION	**SCORE**
Absent	0
Mild	10
Moderate	20
Severe	30
Cardiovascular System	
HEART RATE	**SCORE**
99–109	5
110–119	10
120–129	15
130–139	20
≥140	25
Atrial fibrillation	10
CONGESTIVE HEART FAILURE	**SCORE**
Absent	0
Mild (edema)	5
Moderate (rales)	10
Severe (pulmonary edema)	15
GASTROINTESTINAL	
SYMPTOMS	**SCORE**
Absent	0
Nausea/Vomiting/Diarrhea/Pain	10
Jaundice	20
PRECIPITANT HISTORY	**SCORE**
Present	10
Thyroid Storm Score Interpretation	
TOTAL SCORE	**THYROID STORM**
<25	Unlikely
25–44	Suggestive
≥45	Likely

Ref: Burch HD, 1993.

TABLE 45.2 Treatment of Thyroid Storm

Reduce Thyroid Hormone Synthesis
Propylthiouracil (PO, NG, Rectal): 600–1200 mg daily, or
Methimazole (PO, NG, Rectal, IV): 60–120 mg daily
Reduce Thyroid Hormone Release
Sodium Iodide (IV): 1 gm over 24 hours, or
Potassium Iodide (SSKI, Lugol's - PO): 5 drops QID
Reduce Heart Rate
Esmolol (IV): 500 mcg over 1 minute, then 50–300 mcg/kg/minute, or
Metoprolol (IV): 5–10 mg Q 2-4 hours, or
Propranolol (PO): 60–80 mg Q 4 hours, or
Diltiazem (IV): 0.25 mg/kg over 2 minutes, then 10 mg/minute, or
(PO): 60–90 mg Q 6–8 hours
Glucocorticoid Therapy (Stress Doses for 2–3 Days)
Hydrocortisone 200 mg daily, or
Methylprednisolone 40 mg daily, or
Prednisone 50 mg daily, or
Dexamethasone 7.5 mg daily
Support Circulation, Oxygenation and Ventilation
IV Fluids
Oxygen
Treat Precipitating Cause (critically important)

10. How do patients develop myxedema coma?

Myxedema coma usually occurs in elderly patients who have inadequately treated or untreated hypothyroidism and a superimposed precipitating event. Important events include prolonged cold exposure, infection, trauma, surgery, myocardial infarction, congestive heart failure, pulmonary embolism, stroke, respiratory failure, gastrointestinal bleeding, and drugs, especially those that have a depressive effect on the central nervous system.

11. What are the clinical manifestations of myxedema coma?

Hypothermia, bradycardia, and hypoventilation are common. Blood pressure, although often low, is more variable. Pericardial, pleural, and peritoneal effusions are often found. An ileus and acute urinary retention may be seen. Central nervous system manifestations include seizures, stupor, and coma (Fig. 45.2). Deep tendon reflexes are absent or exhibit a delayed relaxation phase. Typical hypothyroid skin and hair changes are often apparent. A goiter, if present, is a helpful finding. A thyroidectomy scar may also be an important clue.

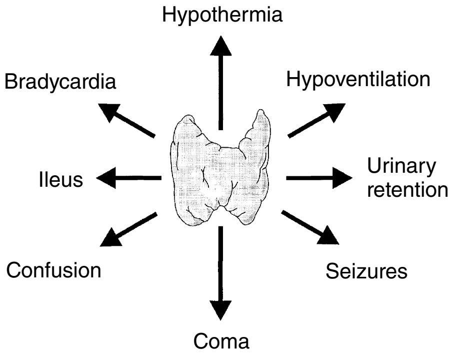

Fig. 45.2 Features of myxedema coma.

12. What laboratory findings suggest myxedema coma?

Serum T_4 (total and free T_4) and T_3 (total and free T_3) are usually low, and TSH is significantly elevated. Other frequent abnormalities include anemia, hyponatremia, hypoglycemia, and elevated serum cholesterol and creatine kinase (CK). Arterial blood gases often reveal carbon dioxide retention and hypoxemia. The electrocardiogram often shows sinus bradycardia, various types and degrees of heart block, low voltage, and T-wave flattening.

13. How is the diagnosis of myxedema coma made?

Myxedema coma is diagnosed based on nonspecific clinical findings, supported by laboratory testing. Table 45.3 provides a useful published and validated scoring system to aid in diagnosis (Popoveniuc G). A different scoring system has been proposed by a separate group (Chiong YV). Although scoring systems are useful, a careful evaluation and sound clinical judgment by an experienced clinician are of paramount importance.

TABLE 45.3 Myxedema Coma Scoring System

Temperature	
HYPOTHERMIA (^{o}C)	**SCORE**
>35	0
32–35	10
<32	20
Cardiovascular-Pulmonary Effects	
FEATURE	**SCORE**
Heart Rate ≥60	0
Heart Rate 50–59	10
Heart Rate 40–49	20
Heart Rate <40	30
Hypotension	20
Cardiomegaly	15
Pulmonary Edema	15
Pericardial/Pleural Effusion	10
Hypoxemia	10
Hypercarbia	10
Other EKG Changes*	10
Central Nervous System Effects	
FEATURE	**SCORE**
Absent	0
Somnolent/Lethargic	10
Obtunded	15
Stupor	20
Coma/Seizures	30
Gastrointestinal Effects	
FEATURE	**SCORE**
Anorexia/Pain/Constipation	5
Decreased Motility	15
Paralytic Ileus	20

TABLE 45.3 Myxedema Coma Scoring System (*Continued*)

Metabolic/Renal Disorders	
FEATURE	**SCORE**
Hypoglycemia	10
Hyponatremia	10
Decreased GFR	10
Precipitating Event	
FEATURE	**SCORE**
Present	10
Myxedema Coma Score Interpretation	
TOTAL SCORE	**MYXEDEMA COMA**
<24	Unlikely
25–59	Suggestive
>60	Likely

*Other EKG Changes: QT Prolongation, Low Voltage, BBB, Nonspecific ST-T Wave Changes.
Adapted from Ref: Popoveniuc G, 2014.

TABLE 45.4 Treatment of Myxedema Coma

Thyroid Hormone Replacement (Rapid)
Levothyroxine 200–300 mcg IV over 5 minutes, or
Triiodothyronine 5–10 mcg IV every 6–12 hours, then
Levothyroxine 50–100 mcg daily PO or IV
Glucocorticoid Therapy (Stress Doses for 2–3 Days)
Hydrocortisone 200 mg daily, or
Methylprednisolone 40 mg daily, or
Prednisone 50 mg daily, or
Dexamethasone 7.5 mg daily
Support Circulation, Oxygenation and Ventilation
IV Fluids
Oxygen
Mechanical Ventilation (if needed)
Passive Rewarming (if severely hypothermic)
Treat Precipitating Cause (critically important)

14. How should patients with myxedema coma be treated?

The goals are to rapidly replace the depleted thyroid hormone pool, replace glucocorticoids, support vital functions, and treat precipitating conditions. The normal total body pool of T_4 is about 1000 mcg (500 mcg in the thyroid, 500 mcg in the rest of the body). Table 45.4 lists the medications and doses commonly used to treat myxedema coma.

KEY POINTS

Thyroid Emergencies

- Thyroid storm is a life-threatening form of severe thyrotoxicosis that usually has a precipitating factor and a high mortality rate if not treated promptly and appropriately.
- When thyroid storm is diagnosed or suspected, treatment with antithyroid drugs, cold iodine, beta-blockers, and stress doses of glucocorticoids, along with management of all precipitating factors, should be promptly initiated.
- Myxedema coma is a life-threatening form of severe hypothyroidism that often has a precipitating cause and a high mortality rate if not promptly and adequately treated.
- When myxedema coma is diagnosed or suspected, management should include rapid repletion of thyroid hormones, stress glucocorticoid doses, and treatment of all precipitating causes.

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CHAPTER 46

Euthyroid Sick Syndrome

Michael T. McDermott

1. What is euthyroid sick syndrome and nonthyroidal illness syndrome?

Euthyroid sick syndrome (ESS) is also known as the nonthyroidal illness syndrome (NTIS). It refers to changes in serum thyroid-stimulating hormone (TSH) and thyroid hormone levels that occur in patients with nonthyroidal illnesses and starvation. It is not a primary thyroid disorder but instead results from changes in thyroid hormone secretion, transport, and metabolism induced by the nonthyroidal illness.

2. When should thyroid tests be ordered in seriously ill patients?

Thyroid tests should be ordered in patients with serious illnesses only when the presence of hyperthyroidism or hypothyroidism is considered likely. Serious nonthyroidal illnesses cause changes in thyroid hormone levels that can easily be confused with thyroid disorders, especially central hypothyroidism. Furthermore, during recovery from serious illnesses, thyroid hormone changes can be mistaken for primary hypothyroidism. Therefore, it is generally best to avoid thyroid testing during or in the first few weeks after recovery from a significant nonthyroidal illness. Considerable experience is often necessary to interpret thyroid tests in these settings.

3. When thyroid testing is necessary in seriously ill patients, which tests are recommended?

A serum TSH level alone is not adequate to distinguish ESS from true thyroid disorders. Serum TSH, free T4, total or free T3, and sometimes total T4 with a T3 resin uptake (T3RU) may all be necessary. Reverse T3 (RT3) measurement, though not indicated for other thyroid conditions, can sometimes be helpful in distinguishing ESS from central hypothyroidism.

4. What thyroid hormone changes occur in patients with mild-to-moderate nonthyroidal illnesses?

Even in mild to moderate nonthyroidal illnesses in the ambulatory setting, serum total and free T3 can decrease to low normal or frankly low levels because of reduced T4 to T3 conversion due reduced deiodinase type 1 (D1) activity. The magnitude of the serum T3 reduction correlates well with the severity of the nonthyroidal illness. Serum free T4, total T4, and TSH levels usually remain within the reference range in the mildest form of ESS (Fig. 46.1).

5. Describe the thyroid hormone changes that are seen in patients with moderate-to-severe nonthyroidal illnesses.

In more severe nonthyroidal illnesses, serum total T3 drops to very low levels, generally in proportion to the underlying illness severity. Serum total T4 levels also drop and the T3RU rises, both due to reduced thyroid hormone binding to transport proteins because of impaired hepatic protein synthesis and circulating inhibitors of protein binding. Serum TSH levels also decrease because of cytokine-mediated suppression of TRH and TSH secretion. TSH secretion can also be inhibited by numerous medications, most notably glucocorticoids and dopamine. Reduced TSH secretion further decreases T3 and T4 levels. Free T4 values are highly variable (normal, decreased, or increased) depending on the underlying illness, concomitant medications, and the assay technique. The most common pattern, therefore, is low TSH, low total T4 and free T4, and very low total and free T3 (Fig. 46.1).

6. Describe the thyroid hormone changes associated with recovery from severe nonthyroidal illnesses.

When patients recover from severe nonthyroidal illnesses, serum TSH levels increase and may be transiently elevated above the reference range. Serum total T3 and total T4 levels begin to increase

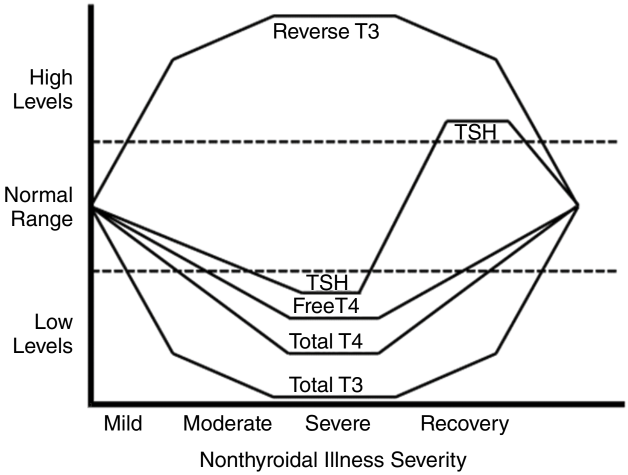

Fig. 46.1 Changes in Thyroid Hormone Levels in Patients With Nonthyroidal Illnesses of Varying Severity and During Recovery.

but may remain low for a while, and free T4 often decreases due to recovery of hepatic production of thyroid hormone–binding proteins. A common pattern during this transition is a mildly elevated serum TSH, low total T4 and free T4, and low total and free T3 (Fig. 46.1).

7. How can euthyroid sick syndrome be distinguished from central hypothyroidism?

In ESS, T3 levels are reduced proportionately more than T4, while in hypothyroidism T4 levels are reduced proportionately more than T3. Furthermore, in ESS the T3RU and RT3 are increased whereas both are low in hypothyroidism. Therefore, a diagnosis of ESS is supported by a low TSH, very low T3, and elevated T3RU and RT3, while central hypothyroidism is suggested by a low TSH, low normal or mildly low T3, proportionately lower T4, and decreased T3RU and RT3 levels. Suspicion of central hypothyroidism should lead to CT or MRI imaging of the hypothalamic–pituitary region and investigation to determine if central adrenal insufficiency is also present.

8. How can recovery from euthyroid sick syndrome be distinguished from primary hypothyroidism?

Thyroid hormone tests during recovery from ESS can show elevated serum TSH levels (transiently) along with low levels of T4 and T3, making this condition difficult to distinguish from mild primary hypothyroidism. Serum T3RU and RT3 levels are not likely to be helpful in the differentiation at this point. Considering the transient nature of thyroid hormone changes during recovery from ESS and the lack of urgency for immediate treatment of mild primary hypothyroidism, it is best to simply repeat thyroid testing 2–3 months after full recovery from the nonthyroidal illness.

9. What is the pathophysiology of euthyroid sick syndrome?

ESS is believed to result from increased circulating cytokines and other inflammation mediators generated by the underlying nonthyroidal illness. These mediators inhibit the thyroid axis at multiple levels, including the hypothalamus (decreased TRH secretion), pituitary gland (decreased TSH secretion), thyroid gland (decreased T_4 and T_3 responses to TSH), transport proteins (decreased thyroid hormone binding), and peripheral tissues (decreased T4 to T3 conversion by tissue deiodinases).

10. What is the function of the deiodinase enzymes?

Deiodinases are selenocysteine enzymes that activate and deactivate thyroid hormones by removing iodine molecules. Deiodinase enzymes have three major subtypes: deiodinase 1 (D1), deiodinase 2 (D2), and deiodinase 3 (D3) (Table 46.1 and Fig. 46.2). D1 converts T4 to T3 in the liver and kidneys and converts reverse T3 (RT3) to diiodothyronine (T2); D1 has a higher affinity for

TABLE 46.1 Deiodinase Enzymes: Selenocysteine Enzymes That Deiodinate Thyroid Hormones

	DEIODINASE 1 (D1)	DEIODINASE 2 (D2)	DEIODINASE 3 (D3)
Substrate	RT3 >> T4	T4 >> RT3	T4 + T3
Tissue	Liver Kidney	Brain Pituitary Fat	Placenta Brain
Function	Clear RT3 ↑ Serum T3	↑ Cellular T3 ↑ Serum T3	Protect Fetus ↓ Cellular T3 Clear T4 + T3

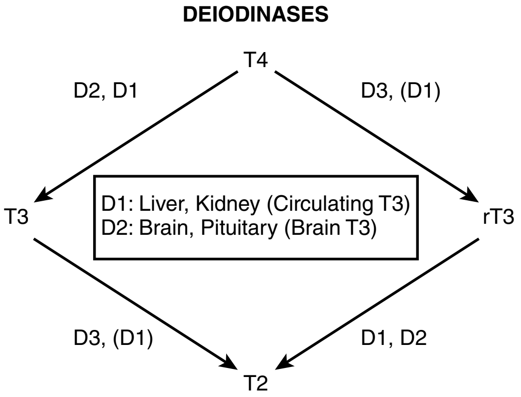
DEIODINASES
T4
D2, D1
D3, (D1)
T3
rT3
D1: Liver, Kidney (Circulating T3)
D2: Brain, Pituitary (Brain T3)
D3, (D1)
D1, D2
T2

Fig. 46.2 Deiodinase Function. *T4,* thyroxine; *T3,* triiodothyronine; *RT3,* reverse triiodothyronine; *T2,* diiodothyronine; *D1,* deiodinase 1; *D2,* deiodinase 2; *D3,* deiodinase 3.

RT3 than for T4. D2 converts T4 to T3 in the brain and pituitary gland; D2 has a higher affinity for T4 than for RT3. D3 converts T4 to RT3 and T3 to T2.

11. What changes in deiodinase function are seen in euthyroid sick syndrome?

D1 activity is significantly reduced and D3 activity is enhanced in ESS. These changes are responsible for the low T3 and high RT3 levels that are characteristic of this condition.

12. Is euthyroid sick syndrome an adaptive mechanism or is it a harmful condition?

Most experts consider ESS to be an adaptive mechanism developed to reduce peripheral tissue energy expenditure during nonthyroidal illnesses. Conversely, some argue that the alterations in circulating thyroid hormone levels may be harmful and may accentuate the effects of nonthyroidal illnesses. The majority favor the former view, but the issue is likely to remain controversial for years.

13. Should patients with euthyroid sick syndrome be treated with thyroid hormones?

Management of ESS is also controversial. Interventional studies have not reported consistent or convincing evidence of benefit from treating ESS with either liothyronine (LT3) or levothyroxine (LT4), and there is some evidence that thyroid hormone treatment may be harmful. LT3 therapy was shown to improve ventricular performance and neuroendocrine profiles in chronic heart failure patients in one randomized controlled trial. Experts agree that large, prospective studies are needed. Therefore, thyroid hormone therapy cannot, at present, be recommended for patients with ESS, except possibly for those with chronic heart failure.

14. Does euthyroid sick syndrome have any prognostic significance?

Low serum T3 and T4 levels have been shown to have significant prognostic value in a variety of serious nonthyroidal illnesses. The degree of serum T3 reduction predicts a poor prognosis in patients with ischemic heart disease, heart valve disease, congestive heart failure, meningococcal sepsis, and numerous illnesses in the intensive care setting. Patients with extremely low serum T3 levels have a high mortality rate.

15. Are levels of thyroid hormone ever elevated in patients with nonthyroid diseases?

Serum T4 may be transiently elevated in patients with acute psychiatric illnesses and various acute medical illnesses. The mechanisms underlying such elevations of T4 are not well understood but may be mediated by alterations in neurotransmitters or cytokines. This condition must be distinguished from true thyrotoxicosis.

KEY POINTS

Euthyroid Sick Syndrome

- Euthyroid sick syndrome is not a thyroid disorder but is instead a group of changes in serum TSH and thyroid hormones that result from cytokines and inflammatory mediators produced during nonthyroidal illnesses.
- Mild euthyroid sick syndrome is characterized by low serum triiodothyronine (T3) levels due to reduced conversion of thyroxine (T4) to T3 by deiodinase enzymes in the liver and other tissues.
- More severe nonthyroidal illnesses cause decreased serum TSH, very low T3, low total T4, variable changes in free T4, increased T3 resin uptake (T3RU), and increased reverse T3 (RT3) due to suppressed pituitary TSH secretion, reduced thyroid hormone binding to transport proteins, and changes in tissue deiodinase activity.
- Transient elevations of serum TSH often occur during recovery from nonthyroidal illnesses.
- Euthyroid sick syndrome appears to be an adaptive response to reduce tissue metabolism and preserve energy during systemic illnesses; therefore, treatment with thyroid hormone is not generally recommended but may be beneficial in patients with chronic heart failure.

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Thyroid Disease in Pregnancy

Linda Anne Barbour and Amy M. Valent

1. How do the physiology of pregnancy, placental function, and fetal demands substantially alter maternal thyroid function and necessitate increased production of thyroid hormone?

The profound hormonal influences that alter maternal physiology, the complete dependence of the fetus on maternal thyroid hormone (TH) in early pregnancy, and the increased metabolic demands of the fetus require remarkable changes in maternal synthesis and thyroid function (Table 47.1). Therefore, pregnant individuals must increase TH production by 25–50% during pregnancy due to the following factors:

- Early in gestation, placental estrogen stimulates the liver to produce two- to threefold higher levels of thyroid-binding globulin (TBG), which necessitates increased synthesis of TH to maintain normal levels of free T4 and free T3 (FT4, FT3).
- Plasma volume expands 30–40%, requiring expansion of the TH pool.
- Placental type 3 deiodinase (D3) activity results in increased T4 metabolism to reverse T3.
- Fetal developmental demands for TH are dependent on sufficient maternal T4 transfer across the placenta prior to 18 weeks.
- Renal clearance of TH increases with the marked increase of glomerular filtration rate (GFR) in pregnancy.

2. Why is thyroid function testing different in pregnancy?

Human chorionic gonadotropin (hCG) stimulates the production of TH and estrogen, increasing total T4 (TT4) and total T3 (TT3) by up to 50%, resulting in dramatic alterations in thyroid function tests (TFTs) compared to nonpregnant norms. Additionally, inconsistent methodologies, differences in population characteristics with respect to iodine status and thyroperoxidase (TPO) antibodies, variable definitions of upper and lower normal percentile ranges, and the absence of gestational-specific norms in most labs challenge the accurate interpretation of TFTs. Many labs and reference ranges do not exclude individuals with positive TPO antibodies when defining norms, resulting in an increase in the upper limit of thyroid stimulating hormone (TSH) by approximately 10–17%, according to the Consortium on Thyroid in Pregnancy (www.consortiumthyroidpregnancy.org). Whether the 95th or 97.5th percentile is used as the upper limit of normal and/or the 2.5th or 5th percentile is used for the lower percentile can make a significant difference in the normal range. Quite strikingly, in a sample of up to 63,198 women in 22 cohorts, the ***upper limit*** of TSH ranged from 2.24–6.02 mIU/L in the first trimester and 2.67–6.15 mIU/L in the second trimester. The ***lower limit*** of FT4 ranged from 0.61–1.03 ng/dl in the first trimester and 0.55–0.89 ng/dl in the second trimester. Third-trimester ranges were limited due to inadequate sample size.

3. Why and how does TSH change in pregnancy?

The alpha subunit of TSH is identical to hCG and the beta unit also shares some sequence homology, and thus hCG can bind weakly and stimulate the TSH receptor. Levels of hCG higher than 50,000 IU/L, achieved by mid-gestation, may increase the FT4 level enough to suppress the serum TSH in at least 20% of normal pregnancies. It is estimated that every 10,000 IU/L of hCG may reduce TSH by 0.1 mIU/L. In one large series, the 95% confidence limits were as low as 0.03 mIU/L in the first and second trimesters and 0.13 mIU/L in the third trimester, levels that are commonly observed among multifetal gestations. Although previous recommendations by the Endocrine Society and American Thyroid Association (ATA) suggested an upper limit of normal for TSH <3.0 mIU/L, the 2017 ATA guidelines recommended that the upper limit of normal for TSH in all trimesters be reduced by about 0.5 mIU/L and that the lower limit be about 0.4 mIU/L less than the nonpregnant range (generally 0.1 mIU/L–4.0 mIU/L). One large

TABLE 47.1 Thyroid Function Tests During Normal Pregnancy

	FIRST TRIMESTER	SECOND TRIMESTER	THIRD TRIMESTER
Total T4	Add 5% per week starting at 7 weeks	1.5 × ↑ by 16 weeks	1.5 × ↑ the remainder of pregnancy
Total T3	Add 5% per week starting at 7 weeks	1.5 × ↑ by 16 weeks	1.5 × ↑ the remainder of pregnancy
T3RU	↓	↓	↓
Free T4 index	Normal	Normal	Usually normal or slightly decreased
TSH	Slightly↓or subtract 0.4 from the lower normal nonpregnancy range and 0.5 from the upper normal nonpregnancy range; typically, 0.1–4.0 mIU/L	Same as first	Same as first
Free T4	Usually, normal	Usually normal or slightly ↓	Usually within the low to normal range or slightly ↓
Free T4 equilibrium dialysis (ARUP)	First trimester 0.7–2.0 ng/dl (nonpregnancy range: 1.1–2.4 ng/dl)	Second trimester 0.7–2.1 ng/dl	Third trimester 0.5–1.6 ng/dl

↑ Increased; ↓, decreased; *T3*, Triiodothyronine; *T3RU*, T3 resin uptake; T4, thyroxine; *TSH*, thyroid-stimulating hormone

study, performed by the Maternal-Fetal Medicine Units Network, screened thyroid function in >97,000 pregnant women before 20 weeks gestation. This study established that the 97.5 percentile TSH level in the first 15,000 women screened was 4.0 mIU/L, prompting the new recommended definition. However, TPO-positive women were not excluded. Although the TSH is lowest in the first trimester or early second trimester when hCG peaks, trimester-specific ranges were not established. Subtracting an absolute number from the nonpregnancy reference range is a reasonable alternative (minus 0.5 mIU/L from the upper range limit and minus 0.4 mIU/L from the lower range limit), but this has not been thoroughly researched. Ethnicity-related differences are also relevant. Black and Asian women have TSH values that are, on average, 0.4 mIU/L lower than in *White* women. Given all of these variables, it is important that the TSH be interpreted in the context of TH levels, despite the assay challenges of these measurements.

4. How does pregnancy change the performance and ranges of total and free assays T4 and T3?

Estrogen increases TBG by two- to threefold beginning a few weeks after conception. Since >99% of T4 and T3 are bound to TBG, the result is an approximately 5% increase per week in TT4 and TT3 starting at week 7 and up to a 50% increase (1.5 times the nonpregnant range) in TT4 and TT3 by week 16. Measurement of the T3 resin uptake (T3RU), which is inversely related to serum thyroid binding capacity, is correspondingly low. The calculated free T4 index (FT4I = total T4 × T3RU) is usually normal. However, the normal ranges for FT4 fall by approximately 30% in the late second and third trimesters of pregnancy, and most commonly used immunoassays do not give pregnancy-specific ranges. An equilibrium dialysis method that offers gestational-specific ranges is more accurate than immunoassays for FT4 but requires the sample to be sent out to a national reference laboratory (Table 47.1). Online solid phase extraction–liquid chromatography/tandem mass spectrometry (LC/MS/MS) is another method to measure FT4 accurately but is usually not available outside of the research context.

The ranges provided by manufacturers for FT4, FT3, TT4, TT3, and TSH have been established using pools of nonpregnant sera. Similar to TT4, only 0.03% of serum TT3 is unbound, resulting in even greater technical challenges in FT3 measures given there is less circulating FT3. An adjusted TT3 level is usually more accurate. In addition to the very high TBG levels, low albumin levels and high nonesterified fatty acids in pregnancy may all affect the FT4 and FT3 immunoassays. A slightly low FT4 in the late second or third trimesters may be normal or may represent true hypothyroidism and should be interpreted in the context of TSH. If TSH is less than 4.0 mIU/L, it is unlikely that the woman has true hypothyroxinemia, as long as she does not have pituitary insufficiency (central hypothyroidism) and does not live in an iodine-deficient region of the world. A TT4 (adding 50% to the upper limit of the normal range) or a measuring FT4 using equilibrium dialysis accompanied by trimester-specific ranges may be useful if the accuracy of FT4 is difficult to clinically correlate.

5. Can commonly used supplements, such as biotin, affect thyroid function laboratory assays?

Excess biotin in the bloodstream can affect laboratory assays that utilize biotinylated antibodies and lead to interference and erroneous test results, especially if the woman has taken biotin within several hours of having her sample taken. Biotin is added as a reagent in many assays but is not used with mass spectrometry (LC-MS/MS) or equilibrium dialysis assays. There are many case reports of misdiagnoses of hyperthyroidism in women taking large doses of biotin (usually ≥10,000 μg) due to interference with biotin-sensitive immunoassays, including those for T4, T3, TSH, thyroglobulin, and TSH binding receptor inhibiting antibodies. The effect can last a couple of days. All women being evaluated for thyroid disorders should be questioned on their use of dietary supplements. If biotin has been used and tests are abnormal, it should be stopped for 3–5 days and thyroid functions retested or a biotin-insensitive assay should be used.

6. What factors may compromise maternal ability to increase thyroid hormone production?

Individuals with limited thyroid reserve due to Hashimoto's thyroiditis, partial thyroid ablation, or surgical resection are often unable to increase TH production during pregnancy and often develop hypothyroidism. Women with inadequate iodine intake may also develop hypothyroidism and goiter.

7. How do iodine requirements change in pregnancy and how can they affect the mother and fetus?

An approximately 40–50% increase in iodine consumption is necessary to support the physiologic changes and fetal demands in pregnancy. Fetal TH synthesis increased maternal TH requirements, and a 50–100% increase in GFR that increases urinary iodine excretion during pregnancy all contribute to the increased need for iodine consumption during pregnancy. Nursing mothers also have higher iodine demands given that the exclusively breastfed infant is entirely dependent on the iodine secreted in maternal milk for TH synthesis. If iodine intake is insufficient, TH production drops, resulting in increased secretion of TSH, which then stimulates thyroid gland growth. Thyroid volume commonly increases by 30% or more during pregnancy in iodine-deficient regions and often does not completely regress after delivery (goiter of pregnancy). In relatively iodine-replete areas, such as the United States, thyroid gland volume may increase by 10–15%, primarily as a result of pregnancy-induced vascular swelling of the gland, but this usually can't be appreciated by palpation. Therefore, any goiter found during pregnancy in an iodine-replete area should be evaluated in the same manner as a goiter occurring outside of pregnancy.

Many European and developing countries with endemic iodine deficiency do not supplement with iodine; therefore, pregnant individuals are at risk of iodine deficiency during pregnancy. When iodine intake is severely deficient, overt hypothyroidism results both in the mother and the fetus, since the fetus also has inadequate iodine to synthesize TH. This is referred to as endemic cretinism, with major adverse neurodevelopmental consequences occurring if severe hypothyroidism secondary to iodine deficiency goes unrecognized and untreated at birth. The WHO and ATA recommendations for total iodine intake are 250 μg/day during pregnancy and 290 μg/day during lactation, compared to 150 μg/day in the nonpregnant state. Iodine insufficiency is an increasing problem in the United States as a result of the popularity and consumption of deiodinated salts (Kosher, Himalayan, sea salts, etc.); the prevalence is estimated to be 10–15%. Because not all salt contains iodine, pregnant and lactating women should take 150 μg of iodine as a supplement or as an element in their prenatal vitamin, especially if they do not use iodinated salt liberally.

8. Do T4, T3, TSH, iodine, and antithyroid drugs (ATDs) cross the placenta?

TSH does not cross the placenta. Significant amounts of T4 cross the placenta; even fetuses with complete thyroid agenesis have approximately 30–40% of the normal amount of TH at birth. However, transplacental transport of TH is limited partly because of the high placental activity of the type 3 mono-deiodinase (D3) that converts T4 to reverse T3 (rT3) and T3 to T2, protecting the fetus from hyperthyroidism to some degree. T4 transported across the placenta is necessary for fetal brain development, especially prior to 16–18 weeks when fetal brain maturation is entirely dependent on maternal T4. Evidence suggests that transthyretin, a circulating thyroid hormone-binding protein synthesized and secreted by the placenta, may provide a mechanism for the delivery of TH to the fetus. To date, a number of TH transporters have been identified in placental tissue, but the relative contribution of each transporter is not yet clear. In contrast to T4, very little T3 crosses the placenta. As a result, T3 preparations (liothyronine, Armour thyroid, or porcine or bovine mixed T4/T3 preparations—the latter available over the counter), should not be used for TH replacement in pregnancy. The fetal brain primarily has T4 receptors and not T3 receptors, underscoring the importance of only using T4 supplementation in pregnancy. Iodine easily crosses the placenta for use by the fetal thyroid, which takes up iodine even more avidly than the maternal thyroid after 10–14 weeks of gestation. Iodine-containing drugs like Amiodarone have the potential to cause iodine overload in the fetus. Because ATDs cross the placenta more easily than T4, the minimum amount of ATDs necessary to keep TH at the upper limits of normal should be prescribed for pregnant women with hyperthyroidism.

9. Do antibodies associated with Graves' disease and Hashimoto's thyroiditis cross the placenta and affect fetal thyroid function?

TSH receptor-stimulating antibodies (thyroid-stimulating immunoglobulins [TSI] and TSH receptor antibodies [TRAb]) cross the placenta. By 18–20 weeks gestation, these antibodies can cause fetal/neonatal hyperthyroidism in pregnancies complicated by Graves' disease, particularly when antibody levels are elevated three times or more. Indications to measure TRAb or TSI during pregnancy include (1) untreated or ATD-treated hyperthyroidism, (2) a previous history of hyperthyroidism with past treatment with radioiodine or total thyroidectomy, (3) a previous history of delivering an infant with hyperthyroidism, and (4) a known history of Graves' disease. It is recommended that both TSI and TRAb be measured because if either antibody is ≥3 times normal, surveillance for fetal Graves' disease is indicated. Although anti-TPO antibodies and antithyroglobulin (TG) antibodies can also cross, they usually have no clinical significance in affecting fetal thyroid function. Very rarely, thyrotropin receptor–blocking antibodies can cause transient neonatal hypothyroidism.

10. Why is maternal thyroid hormone critical to fetal brain development, especially early in pregnancy?

At approximately 12–14 weeks of gestation, the fetal thyroid gland develops, and the hypothalamic-pituitary-thyroid axis begins to function. Before 16 weeks, the fetus relies solely on transplacental delivery of T4, which is critical for neuronal migration, connection, myelination, and synaptogenesis. In early pregnancy, when adequate fetal TH is crucial for normal neurologic development, fetal brain T4 levels reflect maternal levels. TH and type 2 deiodinase (D2) have been observed in the fetal cerebral cortex as early as 5–7 weeks. T4 is taken up by T4 receptors on fetal brain astrocytes and is deiodinated to produce T3. The fetal brain depends on an adequate supply of maternal T4 due to the presence of primarily T4 fetal brain receptors and maternal T3 cannot adequately cross the placenta. This underscores the importance of maternally derived T4 conversion to T3 in the brain and the importance of treating maternal hypothyroidism with T4 only. Babies born with very low T4 at birth due to iodine deficiency or complete agenesis are grossly neurologically normal, as long as levothyroxine is immediately given at birth, but subtle cognitive changes may persist.

11. Later in pregnancy, is fetal thyroid hormone production independent of the mother and how can fetal or newborn thyroid hormone levels be altered?

After 16–18 weeks, the fetal hypothalamic-pituitary-thyroid axis is fairly independent of the mother, with the exception of its complete dependence on adequate maternal iodine stores. ATDs or high levels of TSI or TRAb may affect fetal thyroid function or cause goiter development. T4 and TBG levels increase in the fetus and plateau at about 36–37 weeks of gestation. High fetal levels of rT3 and low T3 levels are maintained throughout pregnancy as a result of high placental D3 activity.

The fetal pituitary-thyroid axis is relatively immature, considering the increased fetal TSH levels relative to the low level of T4 production at birth. At the time of labor and in the early neonatal period, there are dramatic increases in TSH and T4 levels and the capacity of the liver to convert T4 to T3. This TSH surge at birth may not be possible if the fetal pituitary has been exposed to chronic overt maternal hyperthyroidism because the fetal pituitary thyrotropic cells have been suppressed for a substantial time which may result in newborn central hypothyroidism.

12. Does overt hypothyroidism pose a risk to pregnancy?

Hypothyroidism (including subclinical) occurs in approximately 3–4% of pregnancies. Overt hypothyroidism (elevated TSH above the upper limit of normal with decreased serum FT4), sometimes defined as TSH >10 mIU/L, regardless of serum FT4, occurs in approximately 0.5–1%. Untreated overt hypothyroidism with a low FT4 can cause maternal anemia, myopathy, bradycardia, neuropsychologic symptoms, carpal tunnel syndrome, and congestive heart failure. It has also been associated with an increased risk of preterm delivery, pregnancy loss, gestational hypertension, placental abruption, low-birth-weight infants, postpartum hemorrhage, and the possibility of neurodevelopmental delay in the infant. No prospective randomized investigations of treatment of overt hypothyroidism have been performed as this is felt to be unethical. Given that retrospective data strongly support the benefits of treatment in preventing both maternal and fetal adverse pregnancy outcomes, overt hypothyroidism should definitely be treated in pregnancy. Many guidelines consider a TSH ≥10 mIU/L as equivalent to "overt" hypothyroidism in spite of normal FT4 levels.

13. How should overt hypothyroidism be treated?

A full levothyroxine (LT4) replacement dose in pregnancy is approximately 2.0–2.2 µg/kg and a TSH ≥10 mIU/L with a free T4 or TT4 that is low should be immediately treated with a full replacement dose. However, a TSH of ≥10 mIU/L with a normal free T4 or TT4 for pregnancy could be treated with either a mid-range dose of LT4 (75 µg per day) or slightly less than a full replacement dose. Although aggressive replacement of LT4 should not be done in the elderly due to concerns of ischemic heart disease, pregnant women with hypothyroidism are usually of low cardiac risk. Because the half-life of T4 is about 1 week, full repletion of 2 µg/kg may transiently cause mild hyperthyroidism for 1 week, but it is usually well tolerated. Because the fetus is entirely dependent on maternal LT4 until approximately 16–18 weeks, pregnant women with overt hypothyroidism should be treated with near to or full replacement dose to normalize T4 levels as quickly as possible. The TSH should be checked every 4 weeks prior to 18 weeks to target TSH levels between 0.5–2.5 mIU/L (or within the normal TSH range for gestational age) while the fetus is dependent on maternal TH. TSH should be rechecked every 4–6 weeks after dose adjustments and if stable after mid-gestation, it could be checked every 6–8 weeks or at least once in the second and third trimester.

14. Does subclinical hypothyroidism pose a risk in pregnancy and how does the presence of TPO antibodies affect decision-making with respect to treatment?

Subclinical hypothyroidism (SCHypo) is defined as elevated TSH (usually <10 mIU/L) but normal T4 level and is variably associated with adverse pregnancy outcomes. Heterogeneous definitions of an elevated TSH among studies, with or without the presence of TPO antibodies, have contributed to the difficulty in determining the true risk this condition poses to pregnancy. The available evidence most strongly supports an association between SCHypo with miscarriage and preterm delivery, especially with a positive TPO antibody status. A borderline elevated TSH without TPO antibodies may be due to laboratory error but a similar TSH with the presence of TPO antibodies is more likely related to Hashimoto's disease. Most series that support that SCHypo is not associated with adverse fetal or neonatal outcomes have included primarily subjects with minimally elevated TSH levels (<6.0), with no mention of TPO antibodies. It is much less clear whether SCHypo characterized by higher TSH levels of 7–10 and positive TPO antibodies result in similar outcomes. Available data do not definitively support that treatment of women with very mild SCHypo in pregnancy with levothyroxine (LT4) is necessary. Two large multicenter randomized clinical trials (Controlled Antenatal Thyroid Screening Study and Treatment of SCHypo or Hypothyroxinemia in Pregnancy Study) demonstrated no improvement in pregnancy outcomes or cognitive function in childhood with treatment. However, treatment was typically started after the first trimester and often not until 16–18 weeks, when the fetus was already making its own T4. Furthermore, the studies randomized treatment for a relatively low TSH (mean 4–5) and TPO antibody status was unknown for both studies. Thus, the question of whether treatment of SCHypo diagnosed and treated earlier in pregnancy (<16 weeks), with an elevated TSH between 7–10 mIU/L, or with positive TPO antibody status improves outcomes remains unsettled. A meta-analysis of seven RCTs and six observational studies of pregnancies complicated by SCHypo and treated with LT4 found that the use of LT4 was associated with a decreased risk of pregnancy loss (RR = 0.79; 95% CI, 0.67–0.93) but no difference in preterm birth or cognitive outcomes.

15. What are the recommendations for treatment of SCHypo during pregnancy?

Treatment guidelines for SCHypo are not consistent across professional organizations. The ATA recommends treating any woman with a TSH >10 mIU/L and considering treatment for those with TSH levels from 4–10 mIU/L, especially if TPO antibodies are positive. ACOG states that there is insufficient evidence to screen for and treat SCHypo but does not address TPO antibody status, nor the degree of the TSH elevation. Ordering TPO antibodies may delay treatment briefly and the level at which TPO antibodies should be considered positive continues to be controversial. Since a TSH level is considered abnormal if it is above the pregnancy range after subtracting 0.5 mIU/L from the nonpregnancy range and a TSH level >4.0 mIU/L is usually >97.5th percentile for pregnant individuals in the United States, treatment should be considered for women with TSH levels in the 4–10 mIU/L range given the potential benefit and minimal risk regardless of TPO antibody status. Typically, a low dose of LT4 (approximately 50 μg daily) is utilized for the treatment of SCHypo.

Previous recommendations from the Endocrine Society or ATA to consider treatment of individuals with lower TSH levels of 2.5–4.0 mIU/L and positive TPO antibodies lack rigorous data for any clear benefit and may result in overtreatment. Adequately powered RCTs that include a sufficient population of pregnancies with TSH values in the 6–10 mIU/L range with or without TPO antibodies and randomization of LT4 treatment prior to 12 weeks are needed to definitively determine the efficacy of SCHypo treatment in pregnancy on maternal-fetal outcomes.

16. What are the risks of abnormal fetal and neonatal cognitive development among women with overt hypothyroidism in the first trimester?

All newborns in the United States are screened for hypothyroidism because it is well established that infants who have severe congenital hypothyroidism but who then receive TH therapy immediately after birth may have adequate cognitive growth and development. As previously mentioned, fetal brain maturation is dependent on maternal TH prior to 18 weeks and retrospective studies have suggested that infants born to mothers who had untreated overt hypothyroidism during pregnancy may have slightly lower neurodevelopmental testing results.

17. Should all pregnant women be screened for elevated TSH in early pregnancy?

Given the lack of rigorous evidence supporting the treatment of mild SCHypo in pregnancy, ACOG recommends against universal screening for abnormal TSH levels in pregnancy. In its 2017 guidelines, the ATA states that there is insufficient evidence either for or against universal screening for abnormal TSH levels early in pregnancy. However, because of maternal and fetal concerns, some have advocated for universal TSH screening of pregnant women during the first trimester. It has been shown that targeted screening of only high-risk women fails to detect approximately 25–35% of women with elevated TSH values. The ATA recommends that all pregnant women should undergo clinical screening for risk factors for hypothyroidism, and TSH levels should be measured when any of the following risk factors are present:

a. History of hypo- or hyperthyroidism or current signs/symptoms of thyroid dysfunction
b. Known thyroid antibody positivity or presence of a goiter
c. History of head or neck radiation or prior thyroid surgery
d. Age >30 years
e. Type 1 diabetes or other autoimmune disorders

f. History of pregnancy loss, preterm delivery, or infertility
g. Multiple prior pregnancies (≥2)
h. Family history of autoimmune thyroid disease or thyroid dysfunction
i. Prepregnancy obesity (BMI ≥40 kg/m^2)
j. Use of amiodarone or lithium
k. Recent administration of iodinated radiologic contrast
l. Residing in an area of moderate to severe iodine insufficiency

18. Should LT4 treatment be offered to women with a history of miscarriage and with isolated-positive TPO antibodies but normal thyroid function?

Several meta-analyses have found an increased rate of nonrecurrent spontaneous pregnancy loss with odds ratios ranging from 2.3–3.9 in women with isolated TPO antibodies and normal thyroid function. There is data linking thyroid autoimmunity with recurrent pregnancy loss; however, a causal relationship has not been established. Several mechanisms have been proposed to explain the link, including decreased thyroid reserve, altered endometrial cytokine levels, altered trophoblast function, and autoimmunity. It is also possible that TPO antibodies are markers of other autoimmune diseases that could be associated with pregnancy loss. In a meta-analysis of 6 RCTs, LT4 treatment of TPO-positive women who had TSH levels <4 mIU/L did not lower the relative risks of miscarriage, delivery, or live birth, even when started preconception. Two RCTs (Thyroid Antibodies and Levothyroxine Study and the T4 Lifetrial) demonstrated no difference in live birth rates with LT4 treatment versus placebo in women with positive TPO antibodies and normal thyroid function. ACOG states that women with recurrent pregnancy loss should not be routinely screened for TPO antibodies. However, individuals who have elevated TPO antibodies have an approximately 15% risk of developing SCHypo later in pregnancy and a 50% chance of having postpartum thyroiditis (PPT). Therefore, if TPO status is known to be positive, TSH should be rechecked 4–6 weeks after identification, again at 24–28 weeks, and at 12 weeks postpartum. This is important to ensure that the woman does not develop SCHypo or overt hypothyroidism during pregnancy or PPT from the immune transition following delivery.

19. How much do LT4 therapy requirements change during pregnancy and what doses of LT4 should be prescribed?

In up to 75% of pregnant women on full LT4 replacement doses, LT4 requirements increase by 25–50% early in gestation. A full replacement dose of LT4 is approximately 2–2.2 μg/kg in pregnancy compared to 1.6 μg/kg outside of pregnancy. One study suggested that athyreotic women requiring full replacement doses should receive a 25% dose increase as soon as pregnancy is confirmed despite a normal TSH, due to the rapid rise in estrogen-stimulated TBG. This can be done by adding 2 tablets of LT4 per week to the woman's regimen, since the half-life of T4 is about 1 week. Another study confirmed that 85% of athyreotic pregnant women required an LT4 increase of 47% by 16 weeks of gestation. The TSH level should be checked as soon as pregnancy is confirmed. Since the TSH may be mildly suppressed in normal pregnancies due to the thyrotropic influence of hCG, the LT4 dose should not be reduced in response to a low first-trimester TSH unless the T4 is correspondingly high. The TSH should be checked every 4 weeks until approximately 18 weeks when the fetus begins making its own TH, 4–6 weeks after a dose change, and every 6–8 weeks thereafter to target TSH levels of 0.5–2.5 mIU/L. The rationale for a TSH target of <2.5 mIU/L is that the median TSH is lower in pregnancy and it is likely that LT4 requirements will continue to increase.

20. How should the LT4 dose be adjusted after delivery?

The LT4 dose should be reduced immediately after delivery to avoid hyperthyroidism; the TSH level should be checked 6 weeks postpartum. Women who had stable thyroid function prior to pregnancy can be transitioned back to their prepregnancy dose after delivery. Often, postpartum women take several months to return to their prepregnancy weight (or not at all). Therefore, an intermediate dose can be considered between the prepregnancy doses and the third-trimester doses until the weight is lost postpartum, particularly if thyroid function was not stable prior to pregnancy. A rough guide for a full replacement dose outside of pregnancy is approximately 1.6 μg/kg in those with overt hypothyroidism.

21. What is isolated hypothyroxinemia and how is it managed during pregnancy?

Isolated hypothyroxinemia (low serum FT4 with normal TSH) is often simply due to lab error, since FT4 levels actually fall slightly later in pregnancy and immunoassays rarely report gestational-specific ranges; an equilibrium dialysis method may be needed for confirmation. Potential causes of truly isolated hypothyroxinemia during pregnancy include severe iodine deficiency or a primary pituitary lesion. T3 is preferentially synthesized over T4 in people with iodine deficiency. Rarely, isolated hypothyroxinemia may occur because normal T3 levels feedback on TSH, resulting in normal TSH levels. Women with central hypothyroidism from a pituitary cause often have a low FT4 with a normal or slightly low TSH, but it is unusual for this to present for the first time in pregnancy, since pituitary lesions typically affect LH/FSH secretion first, resulting in anovulation. If a woman has central hypothyroidism from pituitary deficiency or is thought to have iodine deficiency as the cause of isolated hypothyroxinemia (rather than lab error), repletion with LT4 and/or iodine should be considered to raise the FT4 or TT4 (adjusted for pregnancy) into the normal range.

22. Why is the use of T3 contraindicated in pregnancy?

Triiodothyronine (T3) should not be used in pregnancy because of the dependence of the fetus on T4 for normal neurological development, the presence of predominately T4 receptors early in the fetal brain, and the poor transport of T3 across the placenta due to placental deiodinases and preferential transfer of T4.

23. What can interfere with LT4 absorption and is there a role for Tirosint if malabsorption is suspected?

The most common cause of an elevated serum TSH in a person on a full LT4 replacement dose (2–2.2 μg/kg in pregnancy) is forgetting to take the medication daily. If this is suspected, recommending a pill box can be useful. Furthermore, it is extremely important to educate the woman that the half-life of LT4 is approximately 1 week, so if a dose or more is missed (up to 7 doses in a week), makeup doses can be taken the next day. Pregnant women should take LT4 and any prenatal vitamins, iron, or calcium supplements at least 4 hours apart. Ferrous sulfate, high doses of calcium, and soy can bind to LT4 and interfere with its absorption and bioavailability. Less frequently, malabsorption from celiac sprue (checking for celiac sprue antibodies may be helpful), gastric bypass, achlorhydria, or other GI conditions can result in requirements that are much higher than the usual full replacement dose. People with GI malabsorption or intolerances may benefit from liquid LT4 or Tirosint gel caps (LT4 without inert ingredients) that may be better absorbed and tolerated.

24. Why is hyperthyroidism in pregnancy commonly misdiagnosed and what is the best diagnostic approach?

Normal pregnancy can produce clinical features that mimic hyperthyroidism, such as heat intolerance, mild tachycardia, increased cardiac output, a systolic flow murmur, peripheral vasodilatation, and a widened pulse pressure. Lab results often demonstrate a suppressed TSH level and increased serum levels of TT_4 and TT_3 (approximately 50% higher than nonpregnant ranges after 16 weeks); this generally does not indicate hyperthyroidism, but instead reflects the thyroid stimulatory effect of hCG and the increase in TBG. Radioisotope scans are contraindicated during pregnancy so the differential diagnosis of hyperthyroidism in pregnancy must be based on the history, physical examination, and lab studies. Occasionally a thyroid ultrasound is helpful if it demonstrates thyromegaly, increased vascular flow, a single nodule, or a multinodular goiter. In women with overt hyperthyroidism and hyperemesis gravidarum, an obstetric ultrasound is indicated to exclude a hydatidiform mole or to identify a multifetal gestation.

25. What is gestational transient thyrotoxicosis?

Gestational transient thyrotoxicosis (GTT) is caused by elevated levels of hCG which binds to the TSH receptor and stimulates TH release. GTT has been reported in 3% of pregnancies in European populations and up to 11% in Asian populations. Posttranslational modification of hCG sialylation can change its' affinity for the TSH receptor and its' half-life in the circulation, thus resulting in elevated TH levels in the first half of pregnancy. HCG levels peak in the first trimester; levels greater than 100,000 IU/mL are commonly associated with GTT during this period.

Although higher hCG levels are commonly seen in pregnancies complicated by hyperemesis gravidarum, multifetal gestations, and molar pregnancies (7–10%), no hCG cutoff level can predict or rule out GTT. It is estimated that 30–60% of women with hyperemesis gravidarum (characterized by persistent nausea and vomiting accompanied by electrolyte derangements or a 5% weight loss) have mild overt hyperthyroidism from GTT. Furthermore, in one series of women with a history of Graves' disease, approximately 25% were thought to have hyperthyroidism mediated by hCG rather than Grave's antibodies in the first trimester. In these cases, hCG tended to be higher (237,000 IU/L versus 133,000 IU/L) and TRAB levels tended to be lower, although hCG levels often overlapped and the two causes can simultaneously occur.

Women with GTT alone should not be treated with ATDs, since the hyperthyroidism is mild and usually resolves by approximately 16–18 weeks, perinatal outcomes are usually normal, and treatment of hyperthyroidism from GTT does not improve outcomes. In fact, inappropriate treatment with ATDs can potentially lead to iatrogenic fetal hypothyroidism. It is not recommended to screen for abnormal TFTs in women with hyperemesis gravidarum unless they have other signs or symptoms of nonhCG causes of hyperthyroidism such as Graves' disease or a goiter.

26. What are the most common causes of overt hyperthyroidism in pregnancy?

Overt hyperthyroidism from non-pregnancy–related causes complicate pregnancy in up to 1% of women, although a higher prevalence of autoimmune thyroid disease was reported during the Covid pandemic. Graves' disease accounts for approximately 85% of overt hyperthyroidism cases that are not hCG-mediated. Other non-pregnancy–related causes include toxic multinodular goiters, solitary toxic adenomas, iodine-induced hyperthyroidism, and less frequently, subacute thyroiditis. Graves' antibody levels are highest in the first trimester and can coexist with GTT. Graves' antibodies typically decrease during the second and third trimesters secondary to the immune suppression of pregnancy, but delivery precipitates antibodies to rebound when immune tolerance shifts back postpartum.

27. How can you distinguish between Graves' disease and GTT during pregnancy?

The distinction between Graves' disease and GTT can be challenging. Like GTT, Graves' disease may present in the first trimester with symptomatic thyrotoxicosis followed by clinical and laboratory improvement in the second and third trimesters due to the immune suppression of pregnancy. Graves alone rarely cause nausea and vomiting. Vomiting in women who are hyperthyroid from GTT is due to very high hCG levels, which also stimulate TH production. A prior history of thyroid dysfunction, symptoms predating pregnancy, and physical exam findings that are characteristic of Graves' disease (diffuse goiter, orbitopathy, pretibial myxedema) or a multinodular goiter are highly suggested nonhCG causes of hyperthyroidism. Elevated levels of TRAb and TSI strongly suggest Graves' disease, being positive in about 95% of women with active Graves' hyperthyroidism. In addition, T3 levels are generally higher in Graves' disease (typically the TT3/TT4 ratio is ≥20:1) and the degree of hyperthyroidism is typically milder (FT4 < 2.5 × elevated) in GTT. Hyperemesis gravidarum can result in a compromised nutritional state, resulting in decreased conversion of T4 to T3 in peripheral tissues. Symptomatic treatment of hyperemesis gravidarum is recommended, sometimes with low doses of beta blockers for GTT. However, women with GTT alone should not be treated with ATDs, since GTT markedly improves or resolves by 16–18 weeks.

28. What are the maternal risks of overt non-hCG–related hyperthyroidism in pregnancy?

Inadequately treated maternal hyperthyroidism can result in weight loss, tachycardia, proximal muscle weakness, anxiety, atrial fibrillation, and thyroid storm. Additionally, suboptimal treatment of hyperthyroidism is associated with increased risks for preeclampsia, preterm labor, and cardiomyopathy. Left ventricular dysfunction can occur with high-output cardiac failure, especially in the presence of superimposed preeclampsia, infection, anemia, or at the time of delivery.

29. What are the risks to the fetus/neonate with inadequately controlled maternal hyperthyroidism in pregnancy?

With the exception of GTT, adverse perinatal outcomes correlate with the severity of maternal thyroid dysfunction among pregnancies complicated by hyperthyroidism. Inadequately treated maternal hyperthyroidism can result in fetal loss, fetal tachycardia, intrauterine growth restriction, premature delivery, placental abruption, and a 9-fold increased incidence of low birth weight;

however, congenital malformations are probably not substantially increased in babies born to mothers with untreated hyperthyroidism. Inadequately treated maternal hyperthyroidism can also suppress the fetal hypothalamic-pituitary-thyroid axis, resulting in temporary central hypothyroidism in the newborn and the inability of the newborn to mount an appropriate TSH response at birth. Limited data suggests poorly controlled maternal hyperthyroidism may be associated with a risk of neurobehavioral disorders later in life.

30. How can pregnant women with Graves' disease be safely treated in pregnancy and avoid the risk of overtreatment from ATDs?

ATDs and the judicious use of beta-blockers until the TT4 is at goal (1.5 times the nonpregnant range) or FT4 levels are in the high-normal range for pregnancy comprise the preferred treatment. Unless the woman has severe T3 thyrotoxicosis, the TT3 is not routinely targeted because T3 doesn't cross the placenta efficiently and TT3 normalization may increase the risk of fetal hypothyroidism, particularly if the FT4 drops into the normal range. Cold iodine is not first-line and radioactive iodine is absolutely contraindicated because I-131 readily crosses the placenta, is concentrated by the fetal thyroid after 10–12 weeks of gestation, and is destructive. However, pregnant women with thyroid storm can be safely treated with cold iodine after propylthiouracil treatment along with hydrocortisone and judicious use of beta-blockers.

31. Should subclinical hyperthyroidism be treated in pregnancy?

No. TSH may remain suppressed in some pregnant individuals throughout pregnancy but this poses no risk. In a series of more than 400 women with subclinical hyperthyroidism, pregnancy outcomes in untreated women were no different from those of women without a suppressed TSH. Furthermore, ATD treatment risks unnecessary exposure to the fetus and the unintended consequence of iatrogenic fetal and newborn hypothyroidism. Normalization of TSH should never be the goal in pregnancy. Therefore, regardless of the etiology (Graves' disease, GTT, multinodular toxic goiter, a warm nodule, etc.), a suppressed TSH level alone without an elevated T4 or T3 should never be treated in pregnancy.

32. Which is preferable in pregnant women, Propylthiouracil or Methimazole?

ATDs should be avoided in the first trimester in cases of very mild overt hyperthyroidism, as both Propylthiouracil (PTU) and Methimazole (MMI) are uncommonly associated with birth defects following fetal exposure during organogenesis (approximately 5–10 weeks). PTU is preferred over MMI in the first trimester for moderate to severe overt hyperthyroidism, since MMI has long been associated with a 2–3% higher risk (compared to controls) of developing congenital malformation such as aplasia cutis, choanal or esophageal atresia, abdominal wall defects, ventricular septal defects, and eye and urinary tract abnormalities. PTU is thought to be safer from a teratogenicity standpoint in the first trimester; a recent study showed that, when given in the first trimester, PTU was associated with a 1–1.5% higher risk of usually more minor congenital malformations such as facial and neck cysts and urinary tract abnormalities. However, the risk of PTU-related hepatotoxicity is higher than MMI. Therefore, switching to MMI in the second trimester is often recommended if it can be done effectively and not compromise optimal control of maternal thyroid function. Due to the paucity of data in pregnancy to support continued use of PTU versus switching to MMI, using PTU in the first trimester for fetal safety and MMI in the second/third trimesters for maternal safety needs to be balanced with maternal thyroid function stability, maternal medication compliance, and side effect profiles.

33. How are PTU and MMI dosed and managed during pregnancy?

The lowest possible doses of PTU and MMI should be given with a goal of maintaining the mother's serum FT4 in the high-normal range or the TT4 approximately 1.5 times the nonpregnancy range. The serum TSH level often remains persistently suppressed in women with FT4 and TT4 levels in these ranges and thus the TSH should never be used to titrate the dose of ATDs during pregnancy. Per the ATA guidelines, in early pregnancy (<10 weeks) women with Graves' disease who require low medication doses (MMI ≤5–10 mg/day, PTU ≤100–200 mg/day) can consider cessation of medication to reduce the small risk for teratogenicity during this short period, but T4 and T3 levels should be checked every 2–4 weeks. Similarly, individuals requiring low doses of PTU in the first trimester are often able to be tapered off later in pregnancy due to the immunosuppression of pregnancy, and switching to MMI is not necessary.

The usual conversion of PTU to MMI is about 20:1 (200 mg PTU is approximately 10 mg MMI), but maternal FT4 or TT4 levels need to be carefully followed because responses may be different. If a woman predominantly manifests T3 thyrotoxicosis, PTU may be superior to MMI because PTU also decreases the conversion of T4 to T3. ATDs cross the placenta better than T4 and given fetal dependence on maternal T4, adjustments of ATDs should be made to keep the FT4 or TT4 levels at the upper limit of normal for pregnancy rather than targeting T3, which crosses the placenta less well. ATD adjustments should be made every approximately 2–4 weeks because the immune suppression of pregnancy often results in the ability to markedly decrease ATD dosing throughout pregnancy. The frequency of TH measures can be liberalized to every 4 weeks in the second and third trimesters if stable.

Approximately 1–3% of newborns exposed to PTU or MMI in utero develop transient neonatal hypothyroidism or a small goiter when PTU or MMI doses are titrated to maintain FT4 at the upper limits of normal (or TT4 adjusted for pregnancy). However, fetal hypothyroidism is fairly frequent if the maternal FT4 levels are allowed to fall into the middle or lower-normal range or if attempts are made to normalize the TSH, which should never be done. Pregnant women should have liver functions checked before starting ATDs and then repeated in the second and third trimesters, since hyperthyroidism can cause elevated LFTs. Women should be advised to report any new symptoms immediately. Both PTU and MMI are associated with a 1% or less risk for agranulocytosis. Thus, women should be counseled to report if they develop a fever or sore throat while on these medications and a CBC should be done at that time.

34. Discuss the role of beta-blockers during pregnancy.

Beta-blockers are indicated to treat symptomatic hyperadrenergic signs and symptoms until ATD therapy has rendered the woman euthyroid. However, beta-blockers should be discontinued when the woman becomes euthyroid or symptoms are improved because they also cross the placenta. They may be useful for treating symptomatic GTT until T4 levels fall. Chronic moderate doses of atenolol have been associated with fetal growth restriction and therefore metoprolol and propranolol are usually favored over atenolol. Beta-blockers may also be useful in women with predominant T3 thyrotoxicosis, since they decrease the conversion of T4 to T3, especially if further ATD treatment is likely to drop the T4 levels into the normal range.

35. Can cold iodine be given during pregnancy?

Although radioactive iodine is completely contraindicated in pregnancy, cold iodine (Lugol's solution or saturated solution of potassium iodide [SSKI]) can be used if a pregnant woman has thyroid storm or hyperthyroidism refractory to other treatments. It may also be given in preparation for surgery in a woman with Graves' who is unable to take ATDs, but the fetus should be monitored for the development of a goiter, and the duration should be limited, if possible, to 3 days.

36. Does surgery have a role during pregnancy?

Surgery is rarely indicated during pregnancy but may be necessary in women who are unable to take ATDs (i.e., because of agranulocytosis) or who are refractory to high doses of ATDs. If necessary, it is best to perform surgery in the second trimester before fetal viability, which is at ~23 weeks. The first trimester may pose a risk of miscarriage, and preterm labor risk is increased when surgery is performed in the third trimester. However, the overall risks to the pregnancy are low, and surgery should not be withheld if it is deemed necessary. Cold iodine is often administered prior to surgery to try to reduce the vascularity of the gland. Plasmapheresis has been shown to be useful in pregnancy to lower TH levels with Graves' disease (as well as to lower TRAb) and to allow safe surgery if ATDs cannot be given.

37. How do Graves' disease antibodies impact the fetus and how is fetal Graves' disease diagnosed?

Approximately 5% of cases of Graves' disease in pregnancy are complicated by fetal or neonatal thyroid dysfunction as a result of very high levels of maternal TSH receptor-stimulating antibodies as measured by the TRAb or TSI assays. The risk may be as high as 20–30% with extremely elevated Graves' antibody levels. Because the transplacental passage of IgG is limited, this condition rarely occurs unless either TSI (assays that are designed to measure the stimulatory activity or stimulatory region of the antibody) or TRAb (assays, which measure TSH receptor antibodies that simply compete with the TSH receptor for binding) remain very high in the second and third trimesters.

TRAb or TSI levels may be high in the first trimester, but often fall with the immune suppression of pregnancy. All pregnant women with Graves' disease or a history of Graves' disease should be tested at 18–20 weeks and if either TRAb or TSI levels are ≥3-fold elevated, fetuses should be screened for thyroid dysfunction by evaluating for the presence of a goiter and fetal growth abnormalities on prenatal ultrasound starting at 20–24 weeks and every 4 weeks or as clinically indicated. Additionally, antenatal fetal surveillance should be initiated once or twice weekly beginning at 32 weeks gestation or earlier for concerns of fetal Graves or obstetric indications. Fetal hyperthyroidism may be accompanied by intrauterine growth restriction, fetal tachycardia, fetal hydrops, craniosynostosis, or advanced bone maturation.

Newer assays that measure TRAb or TSI have not been evaluated in a prospective fashion to rigorously determine their positive predictive value for the development of fetal or neonatal Graves' disease. Until more data is available, the same cut-offs (≥3 times normal) as previously used for older generation assays are recommended for use in counseling. Unfortunately, the TRAb and TSI assays are not always consistent (one may be ≥3 times elevated and the other ≤ 3 times elevated), but if either is ≥3 times elevated, it is judicious to recommend fetal surveillance. All women with Graves' disease or a history of Graves' disease should be tested at 18–20 weeks, since numerous cases of fetal Graves' disease have been reported in mothers previously treated with ablative doses of iodine-131 (^{131}I) and who are taking thyroid replacement, including those who have had a thyroidectomy for Graves' disease. Even if TRAb and TSI levels fall by 20 weeks to <3 times elevated, a growth scan should be done in the third trimester.

38. How is fetal hyperthyroidism due to Graves' disease treated?

Fetal thyroid dysfunction should be confirmed by fetal percutaneous umbilical blood sampling (PUBS) and direct thyroid assay if the cause of the fetal goiter is in doubt. Although TRAb antibodies can rarely be both blocking and stimulating, most cases of maternal hyperthyroidism have stimulating antibodies. In addition, ATDs cross the placenta and increase the risk for fetal hypothyroidism with a goiter, especially if higher doses of ATD are prescribed than necessary to maintain the maternal FT4 or TT4 at the upper limit of the normal pregnancy range.

Treatment of fetal hyperthyroidism consists of giving high doses of PTU to the mother so that sufficient amounts of ATD are delivered into the fetal circulation. MMI has been less well studied but has also been used. LT4 therapy in mothers, who are already hypothyroid from previous I-131 ablation or surgery, readily crosses the placenta to the fetus. Maternal-Fetal-Medicine experts should be consulted for any women with TRAb/TSI levels that are ≥3-fold elevated after 20 weeks or if there are other concerns of fetal Graves' disease.

39. Why is neonatal hyperthyroidism more common than fetal hyperthyroidism in the offspring of women with Graves' disease and should the infant be tested after birth?

Neonatal hyperthyroidism is more common than fetal hyperthyroidism because of the high activity of placental D3, the relatively low serum T3 levels in utero, the immaturity of the fetal pituitary-thyroid axis, and the effects of ATDs on the fetus. TRAb and TSI cross the placenta, since they are IgG antibodies and remain in circulation after birth with the potential to stimulate neonatal thyroid function for up to 3 months. All newborns born to mothers who were treated with ATDs in pregnancy or who had persistently elevated Graves' antibodies in pregnancy should be tested for Graves' antibodies and TH levels. Neonatal hyperthyroidism may manifest as irritability, failure to thrive, hyperkinesis, diarrhea, poor feeding, jaundice, tachycardia, poor weight gain, thrombocytopenia, and goiter. Less commonly, exophthalmos, cardiac failure, hepatosplenomegaly, hyperviscosity syndrome, or craniosynostosis may occur. If the mother had been receiving ATDs during pregnancy, it may take 5–10 days for the neonate to manifest symptoms because of the residual effects of the ATDs on the newborn, so serial testing of the newborn is necessary. The neonatal mortality rate may be as high as 30% if the condition is unrecognized and infants may require ATDs for as long as 3 months or longer until Graves' antibodies wane.

40. What are the pregnancy risks associated with a ^{123}I scan or an ablative dose of ^{131}I?

A woman who receives ^{123}I for a thyroid scan early in pregnancy (<10 weeks) can be overall reassured because the fetus does not develop the ability to concentrate iodine before 10 weeks and the radiation exposure from this isotope is very low, with a half-life of approximately 8 hours. An ablative dose of ^{131}I given early in pregnancy has greater perinatal risks. The half-life of ^{131}I is approximately 8 days (it may circulate up to 40–56 days) and the isotope is more destructive to the fetal thyroid gland. Generally, if the dose is given very early when the fetal thyroid gland is not yet trapping iodine, the risk for fetal hypothyroidism is low. Women should be counseled on the potential risks and any individual of child-bearing age should have a serum pregnancy immediately before receiving radioactive iodine. The fetus should be closely monitored for the development of goiter or hypothyroidism and also be tested after birth.

41. How may the risk to the fetus be minimized if ^{131}I is mistakenly given after 6 weeks of pregnancy?

It may be useful in this situation to give PTU or cold iodine to block the recycling of ^{131}I in the fetal thyroid gland, especially if PTU or cold iodine can be given within 1 week of ^{131}I treatment. Maternal-fetal medicine specialists should be consulted to evaluate the fetus and monitor for concerns of hypothyroidism. The fetus can be diagnosed with hypothyroidism in utero by percutaneous umbilical blood sampling (PUBS), and T4 treatment may be given through amniotic fluid injections or PUBS. All reproductive-age individuals regardless of contraceptive measures, should have a pregnancy test before receiving any dose of ^{123}I or ^{131}I.

42. How should women with Graves' disease be counseled preconceptions about treatment?

Many experts recommend definitive treatment with ^{131}I (after a negative pregnancy test) in a woman of childbearing age who wishes to become pregnant, especially if they have a large goiter and require high doses of ATDs. In multiple series of women given ^{131}I for thyroid cancer therapy, no significant differences in stillbirths, preterm births, low-birth-weight infants, or congenital malformations were reported in subsequent pregnancies. Effective birth control must be established, and women should optimally wait for at least 6 months after establishing a stable euthyroid status before trying to conceive. Individuals with Graves' disease who undergo ^{131}I ablation therapy may have an increase in Graves' antibodies after ablation that continues to be present for one year or greater; these antibodies increase the risk of fetal and neonatal Graves' disease. For individuals with very high TRAb who wish to become pregnant within the next year and who require high doses of ATDs, surgery may be a reasonable option. However, in women who are stable on relatively low-moderate doses of ATDs, these drugs are usually not problematic during pregnancy if they are carefully adjusted as previously described.

43. Describe the natural history of Graves' disease in the postpartum period.

Approximately 70% of postpartum women with Graves' disease relapse, typically at 4–8 months after delivery, but sometimes earlier or later. ATDs almost always need to be reinstituted or increased during this time.

44. Does maternal thyroid status impact lactation?

Several case series and cohort studies have demonstrated that both hyperthyroidism and hypothyroidism can negatively impact milk production and the ability to successfully breastfeed with the improvement of lactogenesis after appropriate therapy. Therefore, it is recommended that lactating women who are experiencing inadequate milk production without other identifiable causes have their TSH assessed for thyroid dysfunction and treatment offered if it is identified.

45. What treatments can be recommended for hyperthyroid women who wish to breastfeed?

Because PTU is more highly protein bound and may cross less efficiently into breast milk than MMI, it was previously recommended that nursing mothers with hyperthyroidism be treated with PTU rather than MMI. However, MMI doses up to 20 mg have been safely used in lactating women without any evidence of neonatal hypothyroidism. Therefore, because of concerns about PTU-induced hepatotoxicity, women can safely nurse as long as these MMI doses are not exceeded. To minimize exposure to the newborn, ATD therapy should continue to target the FT4 and T3 levels at the upper limit of the normal range rather than trying to normalize the TSH which may be suppressed for many months after achieving a euthyroid state. It may be beneficial for lactating women to take their ATD dose immediately after nursing to try to minimize peak effects. Thyroid function tests in neonates may be indicated if a woman is taking >400 mg of PTU or >20 mg of MMI per day and the pediatrician should be aware. Typically, the benefits of lactation greatly exceed the very low risk of ATD exposure to the infant.

46. Can ablative therapy with ^{131}I be offered to lactating women?

Ablative therapy with ^{131}I cannot be offered unless the woman is willing to discontinue lactating, since circulating ^{131}I levels are detectable for approximately 56 days after it is administered. Further, it is recommended that ^{131}I should not be given to lactating women until at least 4 weeks after breastfeeding has ceased to avoid high levels in breast tissue.

47. Can beta-blockers be used in lactating women?

Beta-blockers can be used if needed in lactating women. However, atenolol may produce higher breast milk concentrations than other beta-blockers with rare reports of neonatal bradycardia. The lowest doses of propranolol or metoprolol are preferred agents.

48. How should a thyroid nodule be evaluated during pregnancy?

Hormone effects (estrogen, progesterone, hCG) and relative iodine deficiency likely contribute to the development or possible growth of thyroid nodules during pregnancy. The evaluation of a solitary or dominant thyroid nodule during pregnancy is similar to the approach in the nonpregnant state. Ultrasound is indicated to detect sonographic features suggestive of malignancy (punctate echogenic foci, hypoechoic patterns, irregular margins, taller than wide shape, intra-nodular vascularity, lymphadenopathy) and to evaluate for multiple nodules. If the serum TSH level is normal or elevated, fine needle aspiration biopsy (FNAB) of a nodule is recommended based on size and sonographic appearance, using the same criteria that are used outside of pregnancy.

The ATA 2015 guidelines recommend FNAB of nodules with high and intermediate suspicion patterns if the size is >1 cm, low suspicion pattern if the size is >1.5 cm, and very low suspicion pattern if the size is >2 cm or not at all with clinical observation being an acceptable alternative. The Thyroid Imaging Reporting and Data System (TI-RADS classification) by the American College of Radiology differs slightly in an attempt to avoid unnecessary biopsies, but they have similar diagnostic value in predicting thyroid cancer. Abnormal-appearing cervical lymph nodes should also be targeted for biopsy. Women who have nodules discovered in the last trimester of pregnancy can have FNAB delayed until after delivery, but it is often helpful to make the diagnosis of thyroid cancer during pregnancy so that appropriate planning of surgical treatment can be made. Women with a thyroid nodule and suppressed serum TSH may have a functioning (warm or hot) nodule; these are rarely malignant and FNAB is often nondiagnostic. Therefore, pregnant women with a suppressed TSH and a nodule should undergo a radioisotope scan postpartum to determine whether the nodule is warm or cold before obtaining an FNAB, unless ultrasound features are of high suspicion. An I-123 uptake and scan can be performed in lactating individuals if breastfeeding is interrupted for 48–72 hours to allow clearance of the isotope before resuming breastfeeding. FNAB specimens should be evaluated with the same criteria as used for nonpregnant women.

49. What is the likelihood that thyroid nodules discovered during pregnancy are malignant?

Data suggests that thyroid nodules discovered during pregnancy may have a higher risk of being malignant, but this may reflect sampling and referral bias in pregnancy, since some women receive infrequent care prior to or in between pregnancies. Depending on the population, the incidence of biopsied nodules that are benign is greater than 80%, whereas differentiated thyroid cancer has been found in 5–40% of biopsies.

Most malignant nodules are papillary thyroid carcinoma. There are no prospective studies evaluating the outcomes and prognosis of pregnant women with thyroid nodules of indeterminate cytology. During pregnancy, surgery is usually deferred until postpartum for nodules with indeterminate or suspicious cytology unless they are clinically suspicious for aggressive behavior.

Molecular genetic testing of indeterminate nodules is likely reliable in pregnancy, but this has not yet been validated. Typically, molecular testing of indeterminate nodules can be postponed until after delivery.

50. How should a malignant thyroid nodule be managed during pregnancy?

If cytology suggests or confirms papillary thyroid cancer, the best time to offer a thyroidectomy is in the second trimester to avoid the risk of miscarriage in the first trimester and preterm labor in the third trimester. The risk of preterm labor or adverse fetal outcomes related to surgery performed in the second trimester is exceedingly rare. If the nodule is less than 2 cm, has not rapidly increased in size, and the woman has no cervical lymphadenopathy, it may be reasonable to postpone thyroidectomy until after pregnancy and consider administering LT4 suppression therapy in the meantime, with careful attention to avoiding elevated T4 levels. It is appropriate to administer LT4 to achieve a suppressed TSH level in pregnant women with a recent history of thyroid cancer, thyroid cancer diagnosed in pregnancy, or a highly suspicious thyroid nodule as long as the FT4 or TT4 levels are not increased above the normal range for pregnancy. Disease-specific survival for a malignant nodule has not been shown to be affected by the timing of thyroidectomy (i.e. during pregnancy or immediately postpartum) as long as the nodule is a well-differentiated thyroid cancer and treatment is done within 1 year of diagnosis. However, some evidence suggests that recurrence, based on serum thyroglobulin (Tg) levels or rising Tg antibody titers, may be slightly higher in women who wait to have surgery postpartum compared with women who elected surgery in the second trimester.

51. What is postpartum thyroiditis and who is at risk?

Histologically and pathologically, postpartum thyroiditis (PPT) is considered a variant of Hashimoto's thyroiditis with lymphocytic infiltration. It is associated with HLA-DR3, DR4, and DR5 status, characterized by NK cell activity complement activation, and tissue injury provoked by the immunologic rebound postpartum. PPT occurs in approximately 1 out of 20 postpartum women (5–10%) with a much higher incidence in certain populations. In one series, 25% of women with type 1 diabetes developed PPT; it is therefore recommended that this population be routinely screened in the postpartum period. In another series of 152 TPO Ab+ women detected at 16 weeks, PPT occurred in 50%. Of these, 19% had thyrotoxicosis alone (early transient phase), 49% had hypothyroidism alone, and 32% had thyrotoxicosis followed by hypothyroidism. Postpartum women known to be TPO Ab+, especially those with high titers, should have a TSH test performed at 6–12 weeks and 6 months postpartum, or with symptoms.

52. What are the phases of postpartum thyroiditis and how does the first phase typically present?

Classically, the clinical course of PPT consists of three phases, but not all women manifest each phase. At 1–3 months after delivery, affected postpartum women develop mild thyrotoxicosis due to immunologically mediated destruction of thyroid follicles, resulting in the release of stored TH into the circulation. Women may experience anxiety, irritability, palpitations, fatigue, and insomnia, but commonly this phase does not come to clinical attention. Symptomatic women are best treated with low-dose beta-blockers, which must soon be tapered and discontinued as the thyrotoxic phase spontaneously resolves. The use of PTU or MMI is not indicated because the thyrotoxicosis in these women is caused by the destruction of their glands and not by increased TH synthesis.

53. How can phase 1 of postpartum thyroiditis be distinguished from Graves' disease?

Occasionally, there is a question about the cause of thyrotoxicosis because Graves' disease also commonly appears or exacerbates postpartum. However, the hyperthyroidism of Graves' disease tends to present later (4–8 months postpartum) compared to the thyrotoxic phase of PPT (1–3 months), although overlap occurs. Distinguishing between the two conditions is facilitated by the measurement of TPO antibodies and TRAb or TSI. However, many women with Graves' disease also have TPO antibodies and could also manifest PPT. The ratio of TT3/TT4 is typically higher in Graves' disease (>20:1) compared to PPT, and typically the thyrotoxicosis is more severe in Graves' disease than in PPT. The most definitive test is a 123I-uptake test (high in Graves' disease and low in PPT), if the woman is willing to interrupt lactating for 2–3 days. Both ^{123}I and technetium-99 (99Tc) pertechnetate are excreted into breast milk with an effective half-life of 5–8 and 2–8 hours, respectively. Ultrasound can sometimes suggest Graves' disease versus Hashimoto's (PPT) on the basis of size, vascularity, and heterogeneity of the gland.

54. How does the hypothyroid phase of PPT present and how should it be treated?

More commonly, postpartum women present with stage 2 of PPT, which is characterized by hypothyroidism alone or hypothyroidism following transient thyrotoxicosis (phase 1) at about 4–8 months after delivery. Nonspecific symptoms include fatigue, depression, impaired concentration or memory, dry skin, and weight gain, all of which may be overlooked by the clinician. Symptoms may predate the onset of thyroid function abnormalities in TPO Ab+ women and may persist for some time after a euthyroid state is achieved. Women with abnormal thyroid function tests and symptoms consistent with hypothyroidism should be treated with LT4 replacement for approximately 6–12 months. At that time, discontinuation of LT4 can be attempted as 70–80% of women will return to the euthyroid state by 12 months after delivery. TFTs should then be followed at least annually, since approximately 25% of women will be hypothyroid at 2–4 years, and, in a longer series, approximately 50% of women were hypothyroid 7–9 years later. Women with the highest TPO antibody titers and the most severe hypothyroidism appear to be at the highest risk of developing permanent hypothyroidism. If a woman becomes euthyroid within a year postpartum, they have a high likelihood (70%) of developing PPT after a subsequent pregnancy.

KEY POINTS

- Although universal screening is not recommended by most experts, all women with risk factors for thyroid disease should be screened for thyroid dysfunction in the first trimester of pregnancy.
- All pregnant (250 μg) and lactating (290 μg) women require additional iodine per day, so most benefit from a 150 μg iodine supplement.
- TSH, TT4, and TT3 normal ranges change in pregnancy, and free T4 and free T3 assays by analog methods may be inaccurate, especially in the late second and third trimesters. TT4 and TT3 increase by approximately 50% by 16 weeks; therefore, a TSH range of 0.1–4.0 mIU/L has been advocated throughout pregnancy.
- TH requirements usually increase, beginning in the first trimester, and it is reasonable to increase LT4 doses by 25% in athyreotic women as soon as pregnancy is confirmed.
- Overt hypothyroidism (low T4 or T3 or TSH >10 mIU/L) should be treated with near-full replacement doses of LT4 in pregnancy (approximately 2 μg/kg).
- Treatment of subclinical hypothyroidism should be offered if TSH >4.0–10 mIU/L, especially if TPO antibodies are positive , or TSH levels are 7–10. Treatment is typically with low doses of LT4 (50 μg daily).
- Hypothyroidism should not be treated with T3 or preparations that contain T3, since T3 crosses the placenta less well and the early fetal brain has primarily T4 receptors.
- Although TPO antibodies may be associated with a small increased risk of miscarriage, there is currently insufficient evidence to recommend routine screening and treatment of women with a history of recurrent pregnancy loss if they are positive for TPO antibodies but are euthyroid.
- GTT is almost always associated with severe nausea and vomiting in pregnancy and can cause mild overt hyperthyroidism, but typically resolves by approximately 16 weeks and is not benefited by ATD therapy.
- Graves' disease also commonly manifests in the first trimester and with the immune suppression of pregnancy often improves later in pregnancy but typically exacerbates 4–8 months after delivery.
- Women with Graves' disease or a history of Graves' disease (regardless of previous thyroid ablation or thyroidectomy) should be evaluated for TRAb and/or TSI. If levels are ≥3 times elevated at 18–20 weeks or beyond, the fetus should be monitored for the development of fetal and neonatal Graves' disease.
- Overt hyperthyroidism not due to GTT should be treated with the least amount of ATD possible to keep the T4 at the upper limit of the normal range and T4 and T3 should be checked at the minimum of every 4 weeks while titrating ATDs to prevent fetal hypothyroidism. PTU is preferred over MMI in the first trimester.
- Subclinical hyperthyroidism should never be treated in pregnancy.
- Postpartum thyroiditis occurs in approximately 5% of postpartum women without autoimmune disease and approximately 20–25% of women with type 1 diabetes.

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CHAPTER 48

Psychiatric Disorders and Thyroid Disease

Roselyn I. Mateo and James Vincent Hennessey

1. How is hypothyroidism diagnosed—then and now?

Since the 1888 release of the "Report on Myxoedema" by the Clinical Society of London, it has been known for more than a century that overt clinical thyroid dysfunction can lead to psychiatric problems, which can be treated by reestablishment of normal thyroid hormone levels. Hypothyroidism was fatal back then. The majority of patients had late-stage diagnoses and were frequently plagued by cognitive, neurological, and psychological impairments.

Merely half a century later, Asher reiterated the fact that individuals suffering from profound hypothyroidism may exhibit psychosis, thus the phrase "myxedema madness." Despite the inconsistent presentation, general confusion and disorientation with persecutory delusions and hallucinations were common.

The diagnosis was based on the myxedematous appearance of the patient and not the specific mental symptoms. In fact, prior to the advent of routine laboratory measurements of thyroid-stimulating hormone (TSH) and thyroid hormones, thyroid status was assessed using tools that may have correlated with thyroid dysfunction but were not sufficiently specific to ensure a definitive diagnosis. Asher would use a photograph taken before and after thyroid treatment, with a recognizable change serving as a confirmatory test. Other markers of diagnostic value included blood cholesterol, decreased sleeping heart rate, delay in Achilles' tendon reflex time, and basal metabolic rate. Extremely high and low values correlated well with marked hyperthyroidism and hypothyroidism, respectively. However, Asher commented that the presence of mental changes or respiratory obstruction and other diverse conditions, such as acute hospitalization, nonthyroidal illness, pregnancy, cancer, acromegaly, hypogonadism, and starvation, compromised the accuracy of diagnosis.

In current practice, the standard of care is the measurement of serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) as the primary tests for diagnosing thyroid dysfunction and evaluation of thyroid hormone replacement in patients with primary hypothyroidism.

2. How are hypothyroidism and hyperthyroidism symptoms linked to psychiatric disease?

It is commonly known that overt thyroid function abnormalities can have a substantial impact on mood, emotion, thought processes, and mental state (Joffe, 2006). The symptoms of hyperthyroidism, which may include anxiety, dysphoria, emotional lability, and intellectual dysfunction, can also be seen in both mania and depression (Lekurwale, 2023). The latter is particularly common in older patients presenting with (so-called) apathetic thyrotoxicosis (Hennessey, 1996). Hypothyroid symptoms, as listed in Table 48.1, frequently resemble those of depression. In general, symptoms consistent with the presence of thyroid dysfunction are very nonspecific (Canaris et al., 2000) and must be considered in relationship to the patient's comorbidities (Stewart et al., 1989). The symptoms of documented overt thyroid dysfunction have long been recognized as reversible with proper treatment (Singh et al., 2017), but extensive work considering numerous prospective, placebo-controlled studies examining subclinical hypothyroidism (SCHypo) clearly reveals that no symptom relief would be expected after normalization of TSH with thyroid hormone replacement (Feller et al., 2018) and that the nonspecific symptoms that likely triggered the ordering of thyroid functions tests are not due to low circulating levels of thyroid hormones. Other evidence indicates that there is little correlation between common symptoms seen in primary care practice and abnormal thyroid function abnormalities (Bould et al., 2012); in fact, when considering the differential diagnosis of a most common symptom such as tiredness, thyroid dysfunction does not rise to the level of a causal association while depression far outpaces other physical etiologies in frequency (Stadje et al., 2016). A recent study examining the thyroid function, symptoms, and demographics of over 8000 patients found clear differences between the

TABLE 48.1 Clinical Features Common to Both Thyroid Diseases and Mood Disorders

	HYPOTHYROIDISM	MOOD DISORDERS	HYPERTHYROIDISM
Depression	Yes	Yes	Yes
Diminished interest	Yes	Yes	Yes
Diminished pleasure	Yes	Yes	No
Decreased libido	Yes	Yes	Sometimes
Weight loss	No	Yes	Yes
Weight gain	Yes	Sometimes	Occasionally
Appetite loss	Yes	Yes	Sometimes
Increased appetite	No	Yes	Yes
Insomnia	No	Yes	Yes
Hypersomnia	Yes	Yes	No
Agitation/anxiety	Occasionally	Yes	Yes
Fatigue	Yes	Yes	Yes
Poor memory	Yes	Yes	Occasionally
Cognitive dysfunction	Yes	Yes	Yes
Poor concentration	Yes	Yes	Yes
Constipation	Yes	Sometimes	No

Adapted from Hennessey JV, Jackson IMD. The interface between thyroid hormones and psychiatry. *Endocrinologist*. 1996;6:214–223.

symptoms reported by a normal control population and subjects with overt, untreated hypothyroidism but failed to observe any deviation from control scores when considering those who were categorized as SCHypo (Carle et al., 2021). These authors also concluded that the presence of comorbidities contributed significantly to the burden of symptoms (consistent with hypothyroidism) in this population.

3. Which patients with symptoms consistent with the presence of thyroid dysfunction are typically evaluated with TSH and circulating thyroid hormone levels?

It has been demonstrated that individuals who are referred for thyroid function testing due to a clinical suspicion of thyroid malfunction have significant rates of psychological distress; yet, they are not more likely to have hypothyroidism than people who do not exhibit any symptoms (Bould et al., 2012). Hence, if mild elevations in TSH, consistent with a diagnosis of “subclinical hypothyroidism,” are detected in patients with psychological distress, it is more likely to be a coincidental finding rather than a causal finding. As a result, in the absence of overt hypo- or hyperthyroidism, such individuals would not automatically require therapy because it is unlikely to provide a clinically meaningful change in their nonspecific symptoms.

4. What is the association between subclinical hypothyroidism and depression?

Some observational studies in adults have shown a higher prevalence of depression in subjects with SCHypo, defined as a serum TSH level greater than “normal,” while free thyroxine (FT4) is normal; however, larger and more recent studies have found no differences in depressive symptoms between euthyroid and SCHypo subjects at baseline and when monitored over time. In a recent study by Hirtz et al. (2022), there was no association between SCHypo or quartiles of TSH and FT4 levels in the normal range and a major depressive disorder (MDD) in adolescents, despite potential age–related differences regarding thyroid function and MDD risk.

Kim et al. (2018) conducted a large prospective study in a cohort of 220,545 subjects, without a diagnosis of depression at baseline, who underwent at least two comprehensive health examinations between January 1, 2011, and December 31, 2014. TSH, free triiodothyronine (FT3), and FT4 levels were measured at baseline, and incident depressive symptoms occurred in 7323 (8%)

participants over a mean follow-up period of 2 years. After accounting for covariates, the authors found no association between biochemical SCHypo, here defined as an FT4 within the normal range and TSH >5 mU/L, and incident depressive symptoms. Sensitivity analyses among the participants with SCHypo (n = 4384), further subdivided by TSH levels, showed a similar lack of associations with depression for those with TSH ≤10 mU/L and TSH >10 mU/L. Similarly, there was no association between circulating thyroid hormone levels and the risk of incident depressive symptoms among the euthyroid participants (n = 87,822). This finding was confirmed by Bode (Bode et al., 2021) in a metaanalysis of 25 selected studies including 348,014 participants, where there was an association of depression with overt hypothyroidism but not SCHypo.

In older populations, the predictive value of symptoms to identify patients with significant thyroid dysfunction, especially hypothyroidism, is far less reliable (Carle et al., 2016). In subjects aged 70–82 years, (Blum, et al.2016) conducted a cross-sectional and longitudinal study involving 606 participants without antidepressant medication use. Geriatric Depression Scale 15 (GDS-15) scores at baseline did not differ among participants with SCHypo (defined as TSH levels ≥4.5 mU/L and FT4 within the reference range of 12–18 pmol/L), those with baseline subclinical hyperthyroidism (SCHyper, defined as TSH levels <0.45 mU/L and FT4 within the reference range of 12–18 pmol/L), and those designated as the euthyroid controls. After 3 years, changes in GDS-15 scores did not differ for participants considered to have SCHypo at baseline, while those considered to have SCHyper experienced an increase in GDS-15 scores consistent with the development of depression.

5. What is the impact of mild thyroid dysfunction on performance and survival in old age?

Gussekloo et al. (2004) conducted a study evaluating 599 elderly participants (age 85–89 years at enrollment) who were followed for a mean of 3.7 years. Results showed that baseline serum TSH and FT4 levels were not associated with disability in daily life, depressive symptoms, or cognitive impairment at baseline or during follow-up. Mildly "elevated" TSH levels (age-adjusted expected ranges were not used [see below]) were paradoxically associated with decreased all-cause mortality in both men and women, after adjusting for baseline disability and health status, whereas increasing (endogenous) FT4 levels were associated with increased mortality.

In a more recent metanalysis by Du Puy et al. (2021) looking at 2116 community-dwelling participants aged 80 years and older, participants with thyroid dysfunction at baseline did not have significantly different activities-of-daily-living scores compared with euthyroid participants at baseline and had similar mini mental status exam (MMSE) scores, GDS scores, and grip strength; and there were no differences in the change of these functional measures during 5 years of follow-up. Cognitive function with aging is an important factor in determining overall quality of life (QOL). A multicohort individual participant data analysis assessed cross-sectionally and prospectively if alterations in thyroid function were linked to outcomes of MMSE, executive function, memory, and dementia (van Vliet et al., 2021). Global cognitive function was not significantly impacted by the presence of thyroid dysfunction (both hyper- and hypothyroidism). Executive function curiously seemed to be enhanced in the presence of overt hyperthyroidism and SCHypo, while memory was again better among those with SCHypo (van Vliet et al., 2021). Longitudinally, none of the states of thyroid dysfunction predicted a faster onset of mental function decline (dementia). These authors concluded that their findings did not support "screening" for subclinical thyroid dysfunction in the context of cognitive decline in older adults. Therefore, the general population of the "oldest old" with higher levels of TSH does not appear to experience adverse effects and may have a prolonged life span.

6. What is the association between subclinical hyperthyroidism and depression?

Findings derived from the Caerphilly Prospective Study (CaPS) (Williams et al., 2009), which consisted of 2269 middle-aged men (age 45–59 years) with thyroid dysfunction and a meta-analysis of population-based studies examining thyroid function and mood have shown a positive association (odds ratio [OR] 1.12) between depression and endogenous circulating T4 levels and an inverse association with TSH. Another prospective cohort study (Medici et al., 2014) assessed 1503 elderly Dutch men and women (mean age 70.6 years), who were followed up for 8 years. Those in the lowest TSH tertile (0.3–1.0 mU/L) had more concurrent depressive symptoms and were at a substantially higher risk of developing a depressive syndrome in subsequent years when compared with persons in the highest normal range TSH tertile (1.6–4.0 mU/L). These findings were supported by the first metanalysis by Bode et al. (2022), investigating both SCHyper and overt hyperthyroidism and its statistically significant association with clinical depression in the general population.

Interestingly, empiric treatment with thyroid hormone would be illogical in all of these studies, pointing to depression being more closely related to the presence of hyperthyroidism. This underscores the need to thoroughly document the presence of overt thyroid disease biochemically prior to the initiation of any therapies, as symptoms are simply not enough to initiate or adjust thyroid treatments.

7. What should be considered the normal reference range for serum TSH values?

There are differing opinions and contentions as to what should be accepted as a "normal" TSH reference interval and at what value thyroid treatment should commence. This is of paramount importance for every clinician. Over the years, there have been many studies that have examined the predictive value of various ranges of TSH values to identify abnormal thyroid function and predict a positive response to treatment.

A study by Surks and Hollowell (2007) analyzed the age-specific distribution of serum TSH in a thyroid disease–free population without antithyroid antibodies. In this study, serum TSH concentrations were arbitrarily categorized as <0.4, 0.4–2.49, 2.5–4.5, and >4.5 mU/L. Results from the study showed that the TSH distribution among the age deciles progressively shifted toward higher TSH concentrations with aging: 88.8% of those age 20–29 years compared with 61.5% of those age ≥80 years were in the 0.4–2.49 mU/L range; 6.5% compared with 23.9%, respectively, were in the 2.5–4.49 mU/L range; 2% compared with 12%, respectively, were in the >4.5 mU/L range. TSH is redistributed toward higher concentrations with aging in <30% of the disease-free population. It then raises the question of whether the currently used upper limit of 4.5 mU/L, derived from a composite of all age groups in the population, is appropriate for elderly people.

Fontes et al. (2013) prospectively evaluated 1200 subjects of both genders stratified by age groups and found the association between TSH and age to be highly significant. The median serum TSH level was 1.5 mU/L in people age <60 years, increasing to 1.7 mU/L in those age 60–79 years, and to 2 mU/L for those age >80 years. The upper TSH limit (97.5%) increased from 4.3 mU/L for those age <60 years, to 5.8 mU/L in those age 60–79 years, and to 6.7 mU/L in those age >80 years.

According to the National Health and Nutrition Examination Survey (NHANES) III, in a thyroid disease–free population, which only excluded subjects who self-reported thyroid disease or goiter, the upper normal of serum TSH levels was 4.5 mU/L. A reference group taken from this disease-free population, further excluding pregnancy, those on thyroid active medications, and those having detectable antithyroglobulin antibodies (antiTG) or antithyroperoxidase antibodies (antiTPO), resulted in an upper normal TSH value of 4.12 mU/L. When age was considered, the upper limit of normal TSH values were as low as 3.24 mU/L for disease-free reference subjects age 30–39 years and as high as 7.84 mU/L for subjects age >80 years. The 97.5th percentile of serum TSH appears to increase by 0.3 mU/L for every 10-year age increase after 30–39 years of age. Thus, very mild "elevations" in TSH levels observed in older individuals may reflect a normal physiologic change in TSH with aging rather than being diagnostic of subclinical thyroid dysfunction and that the "normal" (or "expected") range may need to be adjusted with increasing age. These studies consistently show that the distribution of TSH progressively changes with age and that perhaps an age-specific reference range should be applied to prevent overdiagnosis and overtreatment of thyroid dysfunction in more vulnerable older adults who do not have hypothyroidism, as we would not anticipate that thyroid hormone replacement would improve their nonthyroidal symptoms (see Question 9). In fact, some of our colleagues in Europe consider an upper limit acceptable TSH to be represented by dividing the decade of the patient's age by 10 (Goichot et al., 2020), so a 74-year-old would be expected to have a TSH up to 7.0 mU/L without significant thyroid disease and an 85-year-old would likely be expected to have a TSH up to about 8 mU/l.

8. Are there any effects on quality of life with variations in thyroid function within the age-specific range?

A study by Samuels et al. (2016) examined data from the Osteoporotic Fractures in Men (MrOS) Study, a cohort of community-dwelling men age ≥65 years in the United States. The study included 539 men who were not on thyroid medications and underwent detailed testing of QOL, mood, and cognitive function at baseline. This study used gender- and age-adjusted upper reference TSH ranges derived from the NHANES III. The upper limit of normal was considered to be 7.48 mU/L for those age 60–69 years, 9.80 mU/L for those age 70–79 years, and 9.36 mU/L for those age ≥ 80 years. FT4 levels were all within the assay-specific reference range. At baseline, there were no associations between TSH or FT4 levels and measures of QOL, mood, or cognition in the 539 euthyroid men. Over the subsequent 5–8 years, they were tested again, and median QOL, mood, and cognitive measures were relatively unchanged. Baseline thyroid function did not predict changes in any of these outcomes over a mean of 6 years in the 193 men reassessed in the longitudinal analysis. Variations in thyroid function within the age-adjusted laboratory reference range were not associated with variations in QOL, mood, or cognitive function.

9. Does treatment of SCHypo specifically among older individuals lead to resolution of symptoms?

Patients with classical symptoms of overt hypothyroidism and with elevated serum TSH levels combined with low serum FT4 levels should be treated with levothyroxine (LT4), but the decision to treat subjects with SCHypo is controversial. Contrary to traditional thinking, SCHypo is not consistently predictive of a diagnosis that, once treated, is likely to result in clinical improvement. Many patients with depression are screened for thyroid dysfunction and classified as having SCHypo when marginal TSH elevations and normal FT4 levels are present. Among the general population, the estimated prevalence of SCHypo, based on laboratory-suggested TSH cutoffs, is 3–8%, and as the average age of the population increases, so does the frequency of diagnosing SCHypo.

The consequences of SCHypo are different for the elderly compared with younger individuals. In current practice, many people diagnosed with neuropsychiatric symptoms and SCHypo are started on LT4 treatment. They frequently experience no improvement in symptoms, and this, in turn, may lead to multiple increases in LT4 doses, resulting in exogenous thyrotoxicosis, or consideration of combination treatment with LT4 and liothyronine (LT3) (Ross, 2022). Regardless of these interventions, there is still often a failure to reverse symptoms because they are not due to hypothyroidism (Hennessey, 2015).

A study by Jorde et al. (2006) evaluated the relationship of neuropsychological function and SCHypo (defined as serum TSH of 3.5–10 mU/L and normal serum FT4 and FT3 levels) and the effect of LT4 supplementation in a prospective, placebo-controlled, double-blind intervention study over 1 year. Various tests of cognitive function, Beck Depression Inventory, General Health Questionnaire, and a questionnaire on hypothyroid symptoms were used to assess the impact of LT4 intervention. At the end of the study, there were no significant differences in any parameter of cognitive function, emotional function, or hypothyroid symptoms, either at the start of the intervention or at the end of the study, among 69 SCHypo participants.

Another double-blind, placebo-controlled, randomized controlled trial by Parle et al. (2010) was conducted in 94 subjects age ≥65 years. Subjects underwent extensive baseline mood and neurocognitive testing, and then were randomized to either LT4 therapy or placebo; thyroid function tests were performed at 8-weekly intervals for dosage adjustments to achieve TSH within the reference range for subjects in the treatment arm. The serum TSH reference range was 0.4–5.5 mU/L. Cognitive tests were administered at baseline and after LT4 intervention. In the LT4 group, 82% and 84% of the subjects achieved euthyroidism at 6- and 12-month intervals, respectively. Results revealed no significant changes in any of the measures of cognitive function over time and no between-group differences in cognitive scores at 6 and 12 months, thus strengthening the evidence that treating elderly subjects with SCHypo with LT4 replacement therapy fails to improve cognitive function.

Stott et al. (2017) conducted the TRUST (Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism) study, a double-blind, randomized, placebo-controlled, parallel-group trial involving 737 adults who were at least 65 years of age. Study subjects had confirmed serum TSH levels between 4.60 and 19.99 mU/L and FT4 levels within the reference range and were designated as being SCHypo. The subjects who were treated with LT4, compared with those given placebo, showed no change in a hypothyroid symptom score or tiredness score on a thyroid–related quality-of-life questionnaire assessed at 1-year follow-up. Another RCT was conducted in 2019 by Mooijaart, et al, (2019) in elderly SCHypo subjects (aged >80 years) in which LT4 treatment did not have an effect on thyroid symptoms, cognition, gait velocity, cardiovascular disease, or overall mortality.

Multiple studies have now shown no benefit to LT4 treatment of SCHypo diagnosed with non–age-adjusted TSH levels. This may support the concept that using the laboratory TSH cutoffs is not sufficiently specific to identify hypothyroidism as the cause of nonspecific complaints found frequently among those offered thyroid function testing. This is of concern, as the initiation of thyroid hormone may occur in some practice settings, and these therapies are associated with a substantial risk of iatrogenic thyrotoxicosis (Taylor, 2014) with increased rates of atrial fibrillation and bone loss (Mammen et al., 2015).

10. What is the "labeling effect" seen in people with known thyroid dysfunction?

Many hypothyroid patients treated with LT4 report persistent neuropsychiatric symptoms, which may result from a "labeling effect" wherein those who are aware of their thyroid status are more likely to report symptoms. In a report on 30,589 subjects in the Norwegian HUNT cohort who underwent both psychological and thyroid function testing, over 2700 were aware of a personal diagnosis of thyroid dysfunction and 73% had normal thyroid function tests at the time of their evaluation (Engum et al., 2002); 1,479 were treated for and carried a diagnosis of hypothyroidism, and 785 had previously been told they had and were treated for hyperthyroidism. Among the subjects evaluated without a previous diagnosis of thyroid dysfunction, 1526 were biochemically dysthyroid but unaware of this at the time of their completion of a hospital anxiety and depression scale (HADS). Subjects with a history of LT4 use, hypothyroidism, or hyperthyroidism had an increased likelihood of clinically significant depression or anxiety. In fact, those who were aware of a thyroid history were more frequently diagnosed with depression and anxiety on HADS testing (Engum et al., 2002) compared to control subjects with no thyroid function abnormalities and those who were biochemically dysthyroid but were unaware of this fact. The authors concluded that those labeled as having a "thyroid problem," independent of their current thyroid function status, experienced more anxiety and depression symptoms than biochemically dysthyroid subjects who were unaware of their diagnosis. A follow-up study including only individuals with thyroid function considered to be in the normal range observed that those burdened with a thyroid diagnosis reported more fatigue, less vitality, and worse scores on the Short Fatigue Questionnaire even when their thyroid function tests were considered to be normal (Van de Ven et al., 2012). An additional follow-on report from the HUNT study focused on patient-reported self-assessment of their current health as either good or poor. Again, there was a euthyroid control group, a subset who were biochemically hypothyroid but unaware of this, and a group who carried a diagnosis of hypothyroidism and were being treated (Jorgensen et al., 2015). As one might now predict, after seeing the preceding two reports, 72–75% of the controls reported they were in good health, 80% of those who were unknowingly biochemically hypothyroid reported good health, but among those with a known diagnosis of treated hypothyroidism women reported good health 41% less frequently than controls and men 29% less frequently than controls. These three studies document that people diagnosed with thyroid dysfunction seem to feel less well and are more likely to be diagnosed with psychiatric conditions independent of their actual thyroid function.

11. How could euthyroid individuals be labeled as dysthyroid?

This can happen by overutilizing symptoms as reliable diagnostic criteria. In the United States, two recent studies of LT4-dispensing behavior have documented that about 30% of new LT4 prescriptions are written for individuals with normal biochemical markers of thyroid function (Hennessey et al., 2021, Brito et al., 2021). If one combines this figure with the 61.5% of new LT4 prescriptions for people who have SCHypo (Brito et al., 2021), then fully 91.5% of those prescribed thyroid hormone replacement are unlikely to have symptom relief (Silverstein and Grady, 2021). This "unnecessary treatment" is not without consequences such as iatrogenic thyrotoxicosis, pill burden, costs, MD visits, blood work, and the fact that thyroid hormone therapy usually continues lifelong (Silverstein et al., 2021). Additionally, once treating "hypothyroidism," primary care providers may be distracted from pursuing broader differential diagnostic considerations of the actual cause of the patient's symptoms.

It follows that once a physician or other provider has prescribed LT4, the patient believes they are hypothyroid. They now have a search term to further look into their symptoms and unfortunately may encounter misconceptions online. This misleading information is learned, and patients find various offered solutions. All of these recommendations likely assume the patients actually are hypothyroid. This diagnosis is seldom verified by the next physician or provider who is asked for refills, and after this misdiagnostic momentum continues for some time, it is extremely difficult to overcome (Rylander & Guerrasio, 2016).

This process may be perpetuated by the fact that many published studies on the impact of thyroid hormone therapy neither "diagnose nor confirm" the hypothyroid state but only ask subjects if they are ingesting some form of thyroid hormone replacement therapy and assume the diagnosis of hypothyroidism. Additionally, once a person is labeled as hypothyroid in the face of a minimally elevated TSH, the search for alternative explanations for symptoms commonly ceases.

Unfortunately, this sequence of events is likely very frequent. Many published reports result from studies that are now conducted online with motivated patients on thyroid hormone replacement therapy meeting hypothyroidism inclusion criteria based solely on their thyroid hormone use. These reports assess subjective patient-reported outcomes and attempt to make objective assessments with computerized questionnaires. A recent paper reported that people on LT4 report emotional distress (ED) with Depression & Anxiety in 50–63% of cases (Pankowski et al., 2021). Pankowski observed that the severity of ED among subjects participating in their online study was directly correlated to the subject's illness–related beliefs rather than their reported thyroid function assessments. In addition, the subjects' beliefs explained a high proportion of the outcomes, accounting for 30% of the depression and anxiety scores and 16% of the subjects' anger (as measured by HADS), which diminished the subjects reported QOL (Pankowski et al., 2021). A similar online study was undertaken to explore the relationship between hypothyroidism and somatization. Using the patient health questionnaire (PHQ-15), the researchers classified self-identified hypothyroid respondents as meeting the criteria of probable somatic symptom disorder (SSD = PHQ-15 >10) or not meeting this threshold and correlated clinical outcomes (Perros et al., 2023). The presence of SSD was seen more frequently in younger respondents, women, and those who were unemployed. Subjects considered to have SSD were very unhappy with their thyroid hormone replacement therapy, were very dissatisfied with the care they were receiving, and felt that their hypothyroidism had a major impact on their daily life. These SSD ratings correlated very strongly with the number of other comorbidities reported, and there was no clear cut preference for any form of thyroid hormone replacement, although these subjects seemed less dissatisfied with LT3 containing replacement therapies (Perros et al., 2023). The reader is reminded that the DSM-5 category here in the United States, which includes SSD and illness-causing anxiety, is equivalent to the WHO ICD diagnosis of hypochondriasis. Unfortunately, hypochondriasis has consequences with both higher all-cause mortality and more frequent suicide (Mataix-Cols et al., 2023).

This intertwining of a seemingly simple diagnosis of hypothyroidism with these most recently documented psychiatric considerations makes confirming the diagnosis of hypothyroidism much more critical, as it seems that treating the wrong disease with thyroid hormone replacement based on nonspecific symptoms has not only the disadvantage of delaying arrival at the correct underlying cause of a patient's complaints but also the negative impact that patients who are incorrectly diagnosed experience no symptom relief when their actual needs are not addressed.

12. Does LT4 therapy improve symptoms in symptomatic euthyroid subjects?

Pollock et al. (2001), in a randomized, double-blind, placebo-controlled, crossover trial, showed that LT4 was not more effective than placebo in improving symptoms, cognition, and mental health in euthyroid participants with symptoms consistent with hypothyroidism. Subjects taking LT4 had higher serum FT4 concentrations and lower serum TSH levels, suggesting adherence to treatment. Subjects taking placebo had unchanged serum TSH levels. However, LT4 was not effective in improving symptoms, cognition, or mental health in these thyroid-healthy participants. It is clear that thyroid hormone treatment does not alter hypothyroid-like symptoms when administered to people who are not hypothyroid. Therefore, it is important to confirm the presence of overt hypothyroidism prior to diagnosis and treatment if one expects symptomatic relief to occur.

13. Does titration of thyroid hormone therapy to target TSH values to the low-normal range versus the high-normal range have a beneficial effect on symptoms?

Walsh et al. (2006) studied 56 subjects with primary hypothyroidism rendered euthyroid with at least 100 mcg daily of LT4. Thyroid hormone doses were then adjusted to achieve high-normal, mid-normal, and low-normal TSH levels. Well-being was assessed with the General Health Questionnaire (GHQ-28), short form 36 (SF-36), and a thyroid symptom questionnaire at baseline and after 8 weeks at each TSH level. No measurable differences in outcomes were detected across the normal TSH range.

Samuels et al. (2018) analyzed 138 subjects who had adequately LT4-treated hypothyroidism and normal TSH levels. These subjects underwent baseline testing for measures of QOL (SF-36, Hypothyroid Dependent QOL), mood (Profile of Mood States, Affective Lability Scale), and cognition (executive function, memory). They were then randomly assigned to receive an unchanged, higher, or lower LT4 dose in a double-blind fashion, targeting one of three TSH ranges (0.34–2.50, 2.51–5.60, or 5.61–12 mU/L). Doses were adjusted every 6 weeks until TSH was stable and in the target range. TSH levels and neurocognitive measures were reassessed at 6 months. At the end of the study, by intention to treat, mean LT4 doses were 1.50 ± 0.07, 1.32 ± 0.07, and 0.78 ± 0.08 mcg/kg ($P < .001$) and achieved mean serum TSH levels of 1.85 ± 0.25, 3.93 ± 0.38, and 9.49 ± 0.80 mU/L ($P < .001$) in the three arms. Results of this study showed that altering LT4 doses to target TSH levels to the low-normal, high-normal, or slightly above-normal ranges does not affect symptoms, QOL, or mood. On the other hand, cognition was not optimal when the TSH had risen into the 5.6–12 mU/L range. Despite a lack of objective benefit, the subjects preferred what they perceived to be higher doses.

Physicians should be aware that not all cases of SCHypo, which are more commonly diagnosed in the elderly, are indicative of true thyroid failure, and that not all symptoms related to neurocognition and neuropsychiatry can be attributed to SCHypo. Additionally, starting thyroid hormone treatment may not result in meaningful symptom relief and may even cause iatrogenic thyrotoxicosis, which has been shown to significantly increase the risk of atrial fibrillation and skeletal fractures. Rethinking who should get thyroid hormone and whether or not thyroid hormone replacement will affect anticipated clinical outcomes is necessary.

14. What abnormalities of thyroid function tests are found in psychiatric disorders?

Because people with thyroid disease may manifest frank psychiatric disorders that are reversible with thyroid medications, the thyroid axis has been extensively studied in patients presenting with a wide variety of behavioral disturbances. Various abnormalities of thyroid function have been identified, particularly in depression. In most depressed subjects the basal serum TSH, T4, and T3 levels are within the normal range, although in one report a third of such patients were observed to have suppressed TSH values.

About 25% of depressed subjects exhibit a "blunted" TSH response (defined as a TSH rise <5 mU/L) to thyrotropin-releasing hormone (TRH) administration. Although unipolar depression is thought to exhibit a blunted TSH response more frequently than bipolar depression, TRH testing has not been successful in differentiating between the two conditions. Once depression has subsided, the blunted TSH response becomes a "state" marker. It should be noted that TRH for injection is not readily available for clinical use in the United States at this time so performing TRH stimulated TSH studies is not currently an available diagnostic procedure.

15. Describe a mechanism for the blunted TSH response to TRH in affective disorders.

The mechanism for the blunted TSH response to TRH administration in affective disorders is not known; however, glucocorticoids, known to inhibit the hypothalamic–pituitary–thyroid axis, are elevated in depression and could be responsible. This suppressed TSH response is not specific to depression and may also be observed in alcohol withdrawal, starvation, normal aging in males, renal failure, acromegaly, Cushing's syndrome, and hypopituitarism. Blunting may also be seen with the use of some medications, such as levothyroxine, glucocorticoids, growth hormone, somatostatin, dopamine, and phenytoin, all of which have been reported to diminish this response.

16. Can abnormalities in the TSH circadian rhythm be identified in depression?

In normal subjects, serum TSH levels begin to rise in the evening before the onset of sleep, reaching a peak between 11:00 p.m. and 4:00 a.m. In depression, the nocturnal TSH surge is frequently absent, resulting in reduced thyroid hormone secretion, supporting the view that functional central hypothyroidism might occur in some depressed subjects.

17. How often are thyroid antibodies present in the patient with depression?

Although the blunted TSH response to TRH administration was well recognized in depression, it is less clearly appreciated that an enhanced TSH response to TRH may occur in up to 15% of subjects with depression but normal baseline thyroid function test results. The majority of those patients have antithyroid antibodies and this finding may be consistent with the presence of incipient hypothyroidism (Brown & Hennessey, 1989).

When autoimmunity is tested utilizing the antiTPO antibody, rather than the less specific antimicrosomal antibody, the prevalence of autoimmune thyroid disease is even higher. Independent of thyroid function, antiTPO positivity has been associated with depression, anxiety, emotional susceptibility, and impaired social life (Ott, 2011; Watt, 2012).

A recent study analyzing the relationship between thyroid antibody positivity and the clinical management of depression included 12,894 participants in the Danish GESUS study (2010–2013) (Jensen et al., 2022). All subjects had antiTPO antibodies measured at study entry: 1643 were TPO **(+)** that was equal to 12.7% of the study population. A total of 2353 (18%) were identified as "past or current" antidepressant users. This left 10,541 "at risk" for incident antidepressant use (ADU). Over a median follow up of 7.8 years, 783 (7.4%) experienced incident ADU. A total of 579 (4.5%) subjects were using LT4 and 316/579 (55%) of these individuals were TPO (+). Of those on LT4, there were an increased number of smokers; these subjects were more likely to have lower income and education, have more comorbidities, and more frequently were noted to have baseline antidepressant use (Jensen et al., 2022). Over the course of follow-up, TPO antibody status and titer had no impact on ADU but being treated with LT4 did predispose to ADU. In fact, the use of LT4 when antiTPO-antibodies were negative, predicted the highest ADU rate.

18. What is the role of type 2 deiodinase (DIO2) in depression and hypothyroidism?

Thyroid hormones play a critical role in the development and function of the CNS. T3 receptors are widely distributed throughout the brain, and there is much evidence that the thyroid hormone regulates brain function through interaction with the catecholaminergic system. Thyroid hormone action in brain tissue is accomplished through the binding of T3 to its nuclear receptors. Brain T3 is derived from T4 by the action of DIO2, which is located throughout the CNS.

It has been postulated that DIO2 activity in the CNS may be deficient in depression, giving rise to a state of relative brain hypothyroidism coexisting with systemic euthyroidism. Alternatively, DIO2 activity could be suppressed by the elevated serum cortisol levels that occur in depression, stress, and nonthyroidal illness (NTI), promoting preferential conversion of T4 to RT3 by type 3 deiodinase (DIO3) activity; this would result in decreased serum and brain T3 levels and increased RT3 levels. Interestingly, LT3 treatment could potentially be beneficial because T3 is not dependent on transport by transthyretin (which is low in depression) and, therefore, exogenous LT3 therapy is postulated to ensure adequate T3 delivery across the blood–brain barrier to the brain.

19. What is the frequency of elevated thyroid hormone values in people with psychiatric disorders?

Serum T4 and, less frequently, T3 levels may be mildly elevated in about 20% of patients admitted to a hospital with acute psychiatric presentations, including schizophrenia and major affective disorders, but infrequently in those with dementia or alcoholism. Although the basal TSH is typically normal, up to 90% of these patients may exhibit blunted TSH responsiveness to TRH. These results don't seem to be indicative of thyrotoxicosis, and the abnormalities resolve on their own without the need for special treatment within 2 weeks. These phenomena could be caused by central hypothalamic-pituitary-thyroid axis activation, which would increase TSH secretion and raise blood levels of T4.

20. Which medications affect thyroid function and thyroid function tests?

Medications commonly used to treat psychiatric illnesses have been shown to affect thyroid function tests (Table 48.2).

21. How does lithium affect the pituitary–thyroidal axis?

The thyroid hormone's ability to be organified and released from the thyroid gland is disrupted by lithium carbonate, a medication used to treat bipolar disorder. Therapeutic lithium concentrations reduce the thyroid gland's production of T3 and T4 and, at higher (likely toxic) concentrations, may also prevent the uptake of iodine and organification. Suppression of serum T4 and T3 levels, elevations of basal serum TSH values, and exaggerated TSH responses to TRH administration may be

TABLE 48.2 Impact of Psychotropic Medications on Thyroid Function Tests

MEDICATION	MECHANISM	TEST FINDINGS
Lithium carbonate	↓ Thyroglobulin hydrolysis	TSH ↑ (transiently)
T3	↓ T4 and T3 release	Hypothyroidism, goiter
Antipsychotics		
Perphenazine	↑ TBG concentration	↑ T4, nl FT4
Anticonvulsants		
Phenytoin	↑ Hepatic clearance of T4	↓ T4, ± ↓ FT4, nl TSH
Carbamazepine	↓ T4 binding, ↑ hepatic clearance	↓ T4, ± ↓ FT4, nl TSH
Phenobarbital	↑ Hepatic clearance	↓ T4, ± ↓ FT4, nl TSH
Valproic acid	↓ T4 binding (?), ↑ hepatic clearance (?)	↓ T4, ± ↓ FT4, nl TSH
Narcotics		
Heroin	↑ TBG concentration	↑ T4, nl FT4
Methadone	↑ TBG concentration	↑ T4, nl FT4
Miscellaneous		
Amphetamines	↑ TSH secretion (?)	↑ T4, ↑ FT4
Biotin	Competes with biotinylated	↑ T4
	T4 competitive assay for binding with streptavidin Competes with the biotinylated sandwich complex for binding with streptavidin	↓TSH

↑, Increased; ↓, decreased; *FT4*, free T4; *Nl*, normal; *T3*, triiodothyronine; *T3RU*, T3 resin uptake; *T4*, thyroxine; *TBG*, thyroxine-binding globulin; *TSH*, thyroid stimulating hormone.

Adapted from Hennessy JV, Jackson IMD. The interface between thyroid hormones and psychiatry. *Endocrinologist*. 1996;6:214–223; Shrestha RT, Malabanan A, Haugen BR, Levy EG, Hennessey JV. Adverse event reporting in patients treated with thyroid hormone extract. *Endocr Pract*. 2017;23:566–575.

initially observed after a 3-week therapeutic course of lithium carbonate; these abnormalities usually return to normal within 3–12 months, even if the medication is continued (Bocchetta, 2006).

22. What is the most common thyroid disorder in lithium-treated patients?

The most frequent thyroid condition that develops in patients receiving lithium treatment is goiter. On rare occasions, hypothyroidism can also occur, especially in those whose thyroid glands have been damaged by conditions like Hashimoto's thyroiditis and Graves' disease previously treated with 131-I therapy. On the other hand, if patients are thyroid antibody negative and their pretreatment thyroid function is completely normal, hypothyroidism is rare. Lithium may be continued and LT4 added if clinically necessary to treat patients developing hypothyroidism or goiter.

23. How do antidepressant therapies affect thyroid function?

Antidepressants do not generally cause abnormal peripheral thyroid hormone levels but may affect thyroid hormone metabolism in the CNS. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) stimulate the activity of DIO2, which causes increased conversion of T4 into T3 in the brain.

Circulating total T4 and FT4, but not TT3, levels often show a modest decline, although still within the normal range, after treatment with various pharmacologic classes of antidepressants; this also occurs with electroconvulsive therapy. There are case reports of sertraline-, paroxetine- and escitalopram–related asymptomatic hypothyroidism, but more recent studies evaluating fluoxetine and sertraline have shown no clinically significant changes in thyroid function test results.

24. Has thyroxine been used as a sole treatment for depression?

Asher's (1949) report on "myxoedema madness" demonstrated that overt thyroid hormone deficiency resulted in depression that reversed with thyroid extract administration. This led to studies of the role of thyroid hormone therapy alone in the treatment of depression and other psychiatric diseases and open studies of high dose LT4 for refractory bipolar and unipolar depression. When treated with LT4, biochemically euthyroid patients who exhibit symptoms suggestive of hypothyroidism and who are classified as depressed on psychological testing do not show improvement. Interestingly, individuals who exhibit hypothyroidism symptoms but have normal thyroid function tests actually react better to placebos. Despite encouraging early reports of LT3 as a stand-alone treatment, these studies had methodological flaws, so it is not clear how thyroid hormone works on its own to treat depression in the absence of abnormal thyroid function. Research evaluating symptom amelioration following combination LT4/LT3 therapy has also yielded conflicting results.

25. How effective is the combination of LT4 and LT3 in the treatment of neuropsychiatric symptoms of hypothyroidism?

Murray introduced thyroid hormone therapy to the English-speaking clinical world in 1891. From the beginning, this was a treatment based on a combination of T4 and T3 derived from animal thyroid extracts. Variability of the T4 and T3 contents and ratios from batch to batch and brand to brand led to the replacement of "natural" combination therapy with pharmaceutically more precise synthetic LT4 and LT3. Eventually, the simplicity of LT4 monotherapy was adopted as usual therapy and found to be safe and effective. The LT4 dosage was historically titrated based on symptoms until TSH assays became available. During the 1980s, sensitive TSH assays allowed for down titration of LT4 therapy to "normal," which resulted in significant dose reductions of as much as 100 mcg/day. However, once euthyroid, some patients were noted to complain of symptoms consistent with some components of textbook lists of symptoms noted in overt hypothyroidism. Since that time, multiple reports have appeared evaluating the effectiveness of combining LT3 with LT4 to improve neuropsychological outcomes (Bunevictus, 1999; Grozinsky, 2006; Walsh, 2003; Garlow, 2012; Escobar, 2015; Joffe, 2007; Hennessey, 2018). In total, as of the composition of the American Thyroid Association (ATA) guidelines published in 2014, more than 13 studies, 1 review, and 3 metaanalyses examined the relative effectiveness of LT4 versus LT3/LT4 combination therapy on clinical outcomes in hypothyroid patients. Based on these data the ATA concluded that there was insufficient evidence to recommend LT4/LT3 over LT4 monotherapy for the treatment of hypothyroidism (Garber, 2012; Jonklass et al., 2018). Since that time, three more placebo-controlled prospective studies (Kaminski et al., 2016, Shakir et al., 2021; Brigante et al., 2024) and another metaanalysis (Lan et al. Clin Endo 2022) have reported data on this topic. In each of the primary analyses, no advantage of LT4/LT3 over LT4 alone was demonstrated. The exception to this was seen in the secondary analysis of the Shakir study that indicated for the first time a statistically significant impact on QOL and symptoms while on LT4/LT3 or DTE. In the few studies where subjects expressed a preference for LT4/LT3 combinations over LT4 alone, this finding could not be explained by changes in the objective psychological and psychometric tests used, or the biological endpoints that were measured.

26. Is there a role of LT3 and/or LT4 therapy in ongoing antidepressant treatment?

The benefit of adjunctive thyroid hormone is not clear, due to mixed results across studies. A study to investigate the efficacy of T3 addition to paroxetine in major depression was conducted in 2004 (Applehof, 2004) wherein 113 patients with major depressive disorder were randomly assigned to 8 weeks of double-blind outpatient treatment with paroxetine 30 mg with the addition of either low-dose T3 (25 microg), high-dose T3 (25 microg twice daily), or placebo. The response rate (reduction of Hamilton Rating Scale for Depression score > or = 50%) was only 46% in all three treatment arms ($P = .99$). These results did not support a role for T3 addition to selective serotonin reuptake inhibitors in the treatment of nonrefractory major depressive disorder and in fact led to more adverse effects.

In a study by Cooper-Karaz (2007), 124 adult outpatients meeting unmodified *DSM-IV* criteria for major depressive disorder without psychotic features were randomized to receive sertraline hydrochloride plus liothyronine sodium or sertraline plus placebo for 8 weeks. Outcomes that were evaluated included a categorical response to treatment (≥50% decrease in scores on the 21-item Hamilton Rating Scale for Depression from baseline to study endpoint) and remission rate (final Hamilton Rating Scale for Depression score ≤6) as a secondary outcome measure. At the end of the study, intent-to-treat Hamilton Rating Scale for Depression response rates were 70% and 50% in the sertraline-liothyronine and sertraline-placebo groups; remission rates were 58% with sertraline-liothyronine and 38% with sertraline-placebo ($P = .02$; odds ratio, 2.69; 95% confidence interval, 1.16–6.49).

Half a decade later, however, a similar study by Garlow et al. (2012), yielded a contrasting result. They performed an 8-week, double-blind, randomized placebo-controlled clinical trial of 153 adult outpatients with DSM-IV defined major depressive disorder. Patients were treated with sertraline flexibly adjusted for tolerability and in a double-blind fashion with placebo or LT3 (25 mcg/day in week 1 and increasing to 50 mcg/day in week 2). The response was defined categorically as 50% reduction and total score less than 15 in 21-item Hamilton Rating Scale for Depression (HRSD-21) at week 8 and remission as HRSD-21 less than 8. There was no difference between treatment groups at the final assessment; 65% of placebo- and 61.8% of LT3-treated subjects achieved response, and 50.6% of placebo- and 40.8% of LT3- treated patients achieved remission. The mean daily dose at the final assessment of sertraline and LT3, respectively, was 144.7 mg (± 48.7 mg) and 48.2 mcg (± 7 mcg). The median time to respond did not differ between treatment groups. Baseline thyroid function tests did not predict response to sertraline treatment or LT3 augmentation.

Adjunctive treatment with LT4 has been studied less frequently in the treatment of acute depressive disorders, and sample sizes were small. The case for using supratherapeutic doses of LT4 stems from open-label case series and trials. In a small study, Bauer et al. (2016), using PET imaging, reported an improvement in clinical depression outcomes correlating with changes in cerebral metabolic activity, which was achieved using supratherapeutic LT4 augmentation. However, more research is needed in order to examine the effect of thyroid hormone augmentation.

27. Are there genetic indicators that may be implicated in the response to treatment?

As personalized medicine evolves, therapies will inevitably become more directed. Initial research investigating type 1 deiodinase (DIO1), which is important for the hepatic and renal conversion of T4 to T3 to provide T3 for circulation, had suggested that certain DIO1 polymorphisms (SNPs) may be associated with significant LT3 potentiation of SSRIs. Patients with certain SNPs have inherently lower DIO1 enzyme activity and therefore have naturally lower serum T3 levels. Compared with those given placebo, these patients had improved depression scores after 8 weeks of LT3 supplementation in combination with sertraline.

Nonetheless, reported results, so far, have been inconclusive or negative. The Thr92Ala polymorphism in the *DIO2* gene is reported to be associated with many medical conditions including insulin resistance, increased body mass index (BMI), type 2 diabetes, hypertension, bipolar disorder, mental retardation (low IQ), recovery from lung injury, osteoarthritis, and increased bone turnover (Bianco & Kim, 2018). An earlier study focusing on the Thr92Ala polymorphism showed an association with worse baseline General Health Questionnaire (GHQ) scores in LT4-treated patients who had this polymorphism; furthermore, initially these subjects appeared to have had significant improvement in symptoms when treated with LT4/LT3 combination therapy compared with LT4 alone (Panicker et al., 2009). Subsequently, after appropriate correction for multiple tests, these results were declared insignificant (Chaker et al., 2017). A total of eight studies have attempted to detect a beneficial effect of adding LT3 to LT4 in the treatment of patients with the Thr92Ala polymorphism and have found no detectable effect (Appelhof et al., 2005; Wouters et al., 2017; Cho et al., 2017; Carle et al., 2017; Shakir et al., 2021; Jensen et al., 2024; Brigante et al., 2024). Studies on another polymorphism, D2-ORFa-Gly3Asp, have shown no association with measures of health–related QOL, neurocognitive functioning, or preference for combined LT4/LT3 therapy.

There was emerging evidence that perhaps the presence of a combination of the Thr92Ala SNP and a polymorphism in the thyroid hormone transporter MCT10 might be associated with a positive response to the addition of LT3 to LT4 (Carle et al., 2017). Subsequent trials have likewise failed to support this combination as a predictor of positive response to LT3 with LT4 (Jensen et al., 2024; Brigante et al., 2024).

28. What recommendations can be made for thyroid evaluation in patients with psychiatric disorders?

It seems prudent to check the thyroid function in those patients with psychiatric disorders who are at increased risk for thyroid disease to rule out overt thyroid disease as the etiology where very specific treatments would be utilized. Women age >45 years, patients with known autoimmune diseases, individuals with a family history of thyroid disease, and those receiving lithium or suffering from dementia should be screened for underlying thyroid abnormalities. Patients receiving medications known to influence the interpretation of thyroid function tests should have these considered when interpreting the results of testing.

29. Is isolated central hypothyroidism in patients on antidepressant or antipsychotic medications a sign of pituitary disease?

Endocrinologists increasingly receive referrals for what appears to be isolated biochemical central hypothyroidism. A retrospective observational study of 71 patients by Keen et al. (2024) across nine different hospitals in South Wales was done over a 6-year period. The investigators identified a total of 1022 individual patients with what appeared to be central hypothyroidism by a thyroid function test database search. After exclusions, 71 patients who seemed to be free of any thyroid hormone therapy had results that were sufficient to be analyzed for determination of a final pathophysiology of central hypothyroidism. There was no clinically significant pathology found on pituitary imaging; however, a review of medications showed that 65% were taking psychotropic medications. The authors concluded that, in the absence of other pituitary hormone dysfunction or visual field defects, these findings suggest a relationship between patients taking psychotropic medications and the appearance of biochemical isolated central hypothyroidism. The report goes on to hypothesize that this likely occurs through suppression of TSH secretion via antagonism of the dopamine-serotoninergic pathway. Additionally, although they make no recommendation regarding the potential utility of thyroid hormone replacement, they strongly feel that this finding does not warrant hypothalamic-pituitary imaging (Keen et al., 2024).

30. Who should receive thyroid hormone for alleviation of psychiatric symptoms?

It is recommended that LT4 therapy be offered to any depressed patient with overt hypothyroidism (serum TSH level >10 mU/L and low FT4 level), especially if accompanied by increased antiTPO titers (Hashimoto's thyroiditis). Thyroid hormone replacement is likely to alleviate the symptoms of depression in these individuals. Patients who have *DIO2* gene polymorphisms previously were hypothesized to benefit from the addition of LT3 according to one study, but subsequent prospective trials in this situation have overwhelmingly not confirmed this SNP as a theoretical predictor of LT3 response. At this time, genetic testing is not recommended for clinical purposes. Adjuvant LT3 lacks clear evidence of effectiveness in patients with depression refractory to treatment but who have normal systemic thyroid function. If used, questions remain unanswered as to the dosing of LT3 with antidepressants, the duration of treatment, and when to withdraw use.

KEY POINTS

- The symptoms of hypothyroidism are very nonspecific and often mimic those of depression, while those of hyperthyroidism may also be confused with depression, mania, or anxiety.
- Mild elevations in serum TSH levels, consistent with a diagnosis of subclinical hypothyroidism, detected in patients with psychological distress are more likely to be a coincidental finding rather than a causal finding.
- More recent studies have found no difference in depressive symptoms between euthyroid subjects and those with subclinical hypothyroidism when followed over time; some studies have even shown that depression seems more closely related to subclinical hyperthyroidism.
- Not all neurocognitive and neuropsychiatric symptoms should be attributed to subclinical hypothyroidism when present.
- Thyroid hormone treatment usually does not provide significant symptomatic benefits in those diagnosed with subclinical hypothyroidism and may, in fact, lead to iatrogenic thyrotoxicosis with proven risks.
- The use of age-adjusted TSH ranges will likely prevent overdiagnosis of subclinical hypothyroidism and may pave the way to better patient selection for thyroid hormone replacement.
- Normalization of the serum TSH level with levothyroxine (LT4) therapy may completely reverse the neuropsychiatric features of overt hypothyroidism but is far less likely to be effective if the symptoms are not caused by the underlying hypothyroidism.

KEY POINTS—CONT'D

- Approximately 20% of patients admitted to the hospital with acute psychiatric presentations, including schizophrenia and major affective disorders, but rarely dementia or alcoholism, may demonstrate mild elevations in their serum T4 levels and, less often, in their T3 levels; these findings usually resolve within 2 weeks without specific thyroid therapy.
- Based on the results of prospective controlled studies, it would not appear justified to utilize combined LT4 and liothyronine (LT3) treatment in hypothyroid patients who complain of depressive symptoms after biochemical euthyroidism is restored with LT4 therapy. Recent guidelines suggest consideration of a wide spectrum of different diagnostic alternative explanations of the symptoms before consideration of additional treatment with LT3 is contemplated.
- It is difficult to make strong recommendations for or against augmentation therapy due to a lack of clinical research in this field.
- It is recommended that LT4 therapy be offered to any patient with depression who has a reproducibly elevated serum TSH and low serum FT4 levels level, especially if accompanied by positive antiTPO antibody titers.

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Disorders of Puberty

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1. What physiologic events initiate puberty?

The hypothalamic–pituitary–gonadal (HPG) axis is activated twice in postnatal life: in infancy and again at true puberty. Mature gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus secrete GnRH in pulses. GnRH pulses stimulate the pituitary gland to secrete pulses of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), with a relatively greater rise in LH. In response to the secretion of gonadotropins, there is the production and secretion of gonadal hormones, leading to the progressive development of secondary sexual characteristics and gametogenesis. *Central puberty* refers to the reactivation of the HPG axis, which is regulated by kisspeptin and several other neuropeptides that stimulate GnRH neurons. In both sexes, normal progression through puberty requires maturation of gonadal function via the HPG axis as well as increased secretion of adrenal androgens.

2. What are the first signs of puberty?

The first physical sign of HPG activation in males is *gonadarche* or testicular enlargement to a testicular volume of ≥4 mL or length ≥2.5 cm. In females, we cannot easily measure ovarian size; therefore, the first physical sign of HPG activation is *thelarche,* or breast buds, indicating estrogen production.

3. How is pubertal development measured?

Sexual maturity is determined by physical examination and is described in a scale devised by John Tanner in 1969 (Table 49.1). Breast development in females and pubic hair in both sexes progress from Tanner stage I (prepubertal) to Tanner stage V (complete maturation). Testicular volume in males can be measured using an orchidometer, with <4 mL representing prepubertal volumes and ≥4 mL representing pubertal volumes. In addition to the physical examination, the tools to assess pubertal development include the determination of skeletal maturation with radiography of the left hand (bone age), growth velocity, growth pattern, and laboratory studies including gonadotropins, sex hormones, and androgens.

4. What is adrenarche?

Adrenarche refers to the production and secretion of androgens from the adrenal gland: dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), and androstenedione. In typically developing children, signs of adrenarche, such as pubic hair, axillary hair, acne, and body odor, occur at a time similar to that of central puberty. The control of adrenal androgen secretion is not clearly understood, but it appears to be separate from the HPG axis.

5. What is the normal pattern of puberty in boys?

The mean age of gonadarche is 11.8 years, with a range of 9–14 years. Pubic hair and penile enlargement typically occur after gonadarche but occasionally occur earlier because of the production of adrenal androgens. It is not until mid-puberty when testosterone concentrations are rising that boys experience voice change, axillary hair, facial hair, and the peak growth spurt. Spermatogenesis is mature at a mean age of 13.3 years.

6. What is the normal pattern of puberty in girls?

Girls normally begin puberty between ages 8 and 13 years (mean age: 10.4 years for White girls; 9.8 years for Hispanic girls; and 9.5 years for Black girls). The initial pubertal event is thelarche in response to estradiol production by the ovaries, although a small percentage of girls will experience pubic or axillary hair growth first in response to adrenal androgen secretion, which may or may not be true puberty. Unlike in boys, the pubertal growth spurt in girls occurs at the onset of puberty. Menarche usually occurs 18–24 months after the onset of breast development (mean age: 12.5 years). Although most girls have reached about 97.5% of their maximum height potential at menarche, this can vary considerably.

TABLE 49.1 Tanner Stages of Pubertal Development

STAGE CHARACTERISTICS	STAGE CHARACTERISTICS
Girls: Breast Development	Girls: Pubic Hair Development
I. Prepubertal; elevation of papilla only II. Breast buds are noted or palpable; enlargement of areola III. Further enlargement of breast and areola, with no separation of their contours IV. Projection of areola and papilla to form a secondary mound above the level of breast V. Adult contour breast with projection of papilla only	I. Prepubertal; no pubic hair II. Sparse growth of long, straight, or slightly curly, minimally pigmented hair, mainly of labia III. Considerably darker and coarser hair spreading over mons pubis IV. Thick, adult-type hair that does not yet spread to the medial surface of the thighs V. Hair adult in type and distributed in a classic inverse triangle and medial thighs
Boys: Genital Development	Boys: Pubic Hair Development
I. Prepubertal; testicular length <2.5 cm II. Testes >2.5 cm in longest diameter, scrotum thinning, and reddening III. Growth of penis in width and length and further growth of testes IV. Penis further larger, with enlarged testes; darker scrotal skin color V. Genitalia adult in size and shape	I. Prepubertal; no pubic hair II. Sparse growth of slightly pigmented, slightly curly pubic hair, mainly at the base of the penis III. Thicker, curlier hair, spread to mons pubis IV. Adult-type hair that does not yet spread to the medial surface of the thighs V. Adult-type hair spread to medial thighs

Data from Marshall WE, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291–303; Marshall WE, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45:13–23.

7. What controls the pubertal growth spurt?

In both boys and girls, the pubertal growth spurt is primarily controlled by estrogen. In both sexes, gonadal (and adrenal) androgens are aromatized to estrogens. Estrogens augment growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secretion. Estrogens also suppress osteoclast activity and prolong the life span of osteoblasts and osteocytes. Estrogen is particularly important at the growth plates, causing epiphyseal fusion and linear growth cessation by the end of puberty. Androgens have a small independent role in linear growth and maintenance of adequate bone mineral density.

8. What is precocious puberty?

Precocious puberty is defined as pubertal development occurring below the limits of age set for the normal onset of puberty. In girls, this is pubertal signs before age 8 years. For boys, precocious puberty is pubertal signs occurring before age 9 years.

9. Why does precocious puberty matter?

The most important reason to evaluate early pubertal signs is to rule out an underlying pathologic etiology that would need treatment, such as a tumor or genetic condition. Precocious puberty can also lead to short adult height because of premature epiphyseal fusion and psychosocial stress. If there is no concerning etiology and predicted height is not concerning, precocious puberty may not require extensive evaluation or treatment.

10. How is precocious puberty evaluated?

Evaluation of precocious puberty begins with a thorough history, including timing of onset of pubertal signs, rate of progression, exposure to exogenous steroids or estrogen receptor agonists (e.g., lavender or tea tree oil), presence or history of central nervous system (CNS) abnormalities, and pubertal history of other family members. A physical examination should be performed, with a focus on Tanner staging and neurologic signs. Height measurements should be plotted on a growth chart to determine the growth pattern, and linear growth velocity should be calculated. Radiography of the left hand and wrist is helpful to determine skeletal maturity (bone age). Depending on this initial assessment, laboratory testing and/or imaging may be needed. Fig. 49.1 provides a simplified flow diagram that can be useful when evaluating a child with precocious puberty.

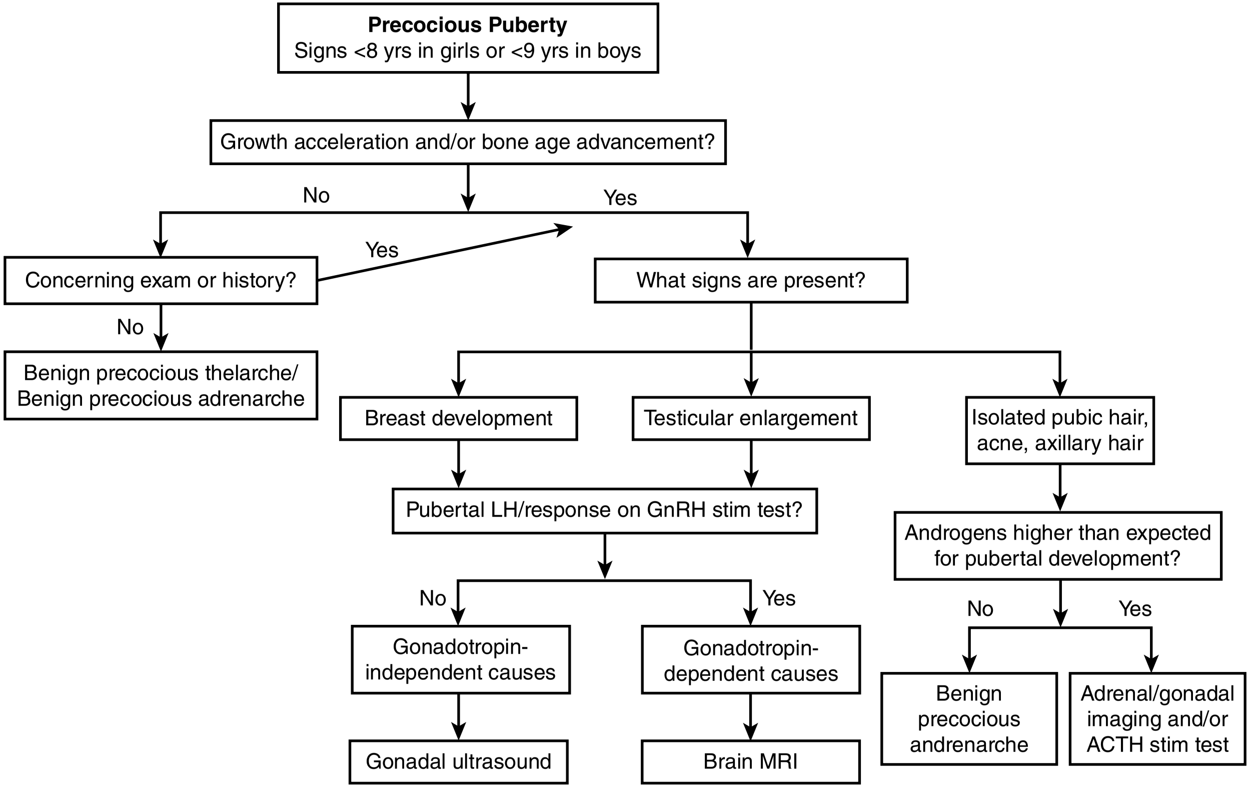
Precocious Puberty
Signs <8 yrs in girls or <9 yrs in boys
Growth acceleration and/or bone age advancement?
No
Yes
Concerning exam or history?
Yes
No
Benign precocious thelarche/
Benign precocious adrenarche
What signs are present?
Breast development
Testicular enlargement
Isolated pubic hair, acne, axillary hair
Pubertal LH/response on GnRH stim test?
No
Yes
Gonadotropin-independent causes
Gonadotropin-dependent causes
Gonadal ultrasound
Brain MRI
Androgens higher than expected for pubertal development?
No
Yes
Benign precocious andrenarche
Adrenal/gonadal imaging and/or ACTH stim test

Fig. 49.1 Evaluation of precocious puberty. *ACTH*, Adrenocorticotropic hormone; *GnRH*, gonadotropin-releasing hormone; *MRI*, magnetic resonance imaging; *stim*, stimulation.

11. What is GnRH-dependent (central) precocious puberty, and how is it diagnosed?

Central precocious puberty (CPP) involves activation of the GnRH pulse generator, an increase in gonadotropin secretion, gonadarche, and a resultant increase in the production of sex steroids. Consequently, the sequence of hormonal and physical events in CPP is identical to the progression of normal puberty. CPP is much more common in girls than in boys. The GnRH stimulation test is the single most important test to diagnose CPP. A child with CPP will have a predominant LH response to a single dose of a GnRH agonist (leuprolide). Measurement of random gonadotropins may not be helpful because of the overlap between prepubertal and early pubertal values. If nonstimulated gonadotropins are obtained, an early-morning sample measured on a third-generation assay will be more likely to identify early pubertal LH concentrations.

12. What causes CPP?

In the large majority of cases, CPP is idiopathic, especially in girls. CPP can also be caused by any CNS disturbance that disrupts the balance regulating the GnRH pulse generator. This includes structural disruptions, such as brain tumors and preexisting malformations. Often, there will be other signs of a CNS lesion, but occasionally precocious puberty can be the presenting sign. Certain genetic conditions or inherited single-gene mutations can also cause CPP.

13. When is brain imaging indicated?

Girls younger than 6 years of age and boys of any age who are diagnosed with CPP should undergo a magnetic resonance imaging (MRI) study of the brain to evaluate for CNS lesions. It is much less likely that an abnormality will be found in girls between ages 6 and 8 years, so the need for an MRI in this age group should be assessed on an individual basis.

14. How is CPP treated?

Children with CPP can be treated with long-acting GnRH agonists, such as leuprolide or histrelin. GnRH agonists disrupt the endogenous pulsatile secretion of GnRH, thus downregulating pituitary GnRH receptors and decreasing gonadotropin secretion. The most important clinical criteria for GnRH agonist therapy is the documented progression of pubertal development, which is based on the recognition that many girls with CPP, especially those between ages 6 and 8 years, have a slowly progressive form and reach normal adult height without any intervention. With GnRH agonist treatment, physical changes of puberty regress or cease to progress, linear growth reverts to the prepubertal rate, and skeletal maturation slows. Projected final adult height often increases because of the slowing of skeletal maturation. GnRH agonists can be given as depot intramuscular injections, or by placement of a small implant under the skin. Children on GnRH agonists should be monitored every 4–6 months to evaluate for pubertal regression or treatment failure. After discontinuation of therapy, pubertal progression resumes, and normal rates of fertility are expected.

15. What is GnRH-independent (peripheral) precocious puberty, and how is it diagnosed?

Peripheral precocious puberty occurs independent of gonadotropin secretion. Early autonomous production of sex steroids from the adrenal glands or gonads can result in peripheral precocious puberty. Basal serum FSH and LH are low (often suppressed), and the LH response to GnRH stimulation is not in a pubertal range. There are numerous etiologies of peripheral precocious puberty (Box 49.1), but these conditions are much less common than CPP. Evaluation for a specific diagnosis will depend on whether signs of androgens or estrogens are present.

16. How is peripheral precocious puberty evaluated?

In girls with signs of estrogen production without CPP, pelvic ultrasonography can be performed to evaluate for an ovarian cyst or tumor, as well as the size of the uterus and endometrial stripe (particularly if vaginal bleeding is present).

In boys or girls with signs of adrenarche (without testicular enlargement in boys), evaluation should include laboratory studies for nonclassic congenital adrenal hyperplasia (CAH) and adrenal tumors. Serum 17-hydroxyprogesterone, testosterone, DHEA-S, and androstenedione levels should be obtained, and, depending on the situation, possibly adrenocorticotropic hormone

BOX 49.1 Clinical Findings in Girls With Turner Syndrome

PHYSICAL FEATURES	FREQUENCY (%)
Short stature	95–100
Increased upper-to-lower segment ratio	97
Short neck	40
Webbed neck	25
Low posterior hairline	40
Micrognathia	60
High-arched palate	35
Epicanthal folds	10
Strabismus	15
Ptosis	10
Cubitus valgus	50–80
Short fourth metacarpals	35
Madelung deformity	5
Edema of hands and feet	25
Fingernail dysplasia/hypoplasia	5
Scoliosis	12
Genu valgum	35–86
Multiple pigmented nevi	25
Congenital Anomalies	
Bicuspid aortic valve	14–34
Coarctation of the aorta	7–14
Renal aplasia	3
Horseshoe kidney	10
Abnormal position or duplication of the renal pelvis/collecting system	15
Physiologic Features	
Otitis media	60
Delayed puberty (no thelarche)	70
Primary amenorrhea	90
Infertility	95
Hypertension	50
Thyroiditis and hypothyroidism	15–30
Alopecia	5
Vitiligo	5
Celiac disease	8
Glucose intolerance	15–50
Type 2 diabetes	10

Data from Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177(3):G1–G70.

(ACTH)–stimulated steroid intermediates (e.g., 17-hydroxyprogesterone, 17-hydroxypregnenolone, 11-deoxycortisol). With elevated adrenal androgen levels suggestive of a tumor, imaging of the adrenal glands should be pursued. Genetic testing for CAH may be helpful, particularly if the biochemical testing is nondiagnostic.

In boys with testicular enlargement but a prepubertal response to a GnRH stimulation test, human chorionic gonadotropin (hCG) and testosterone should be measured. Asymmetric or unilateral enlargement of the testes suggests a Leydig cell tumor and testicular ultrasonography should be performed.

17. What is McCune-Albright syndrome, and how is it treated?

McCune-Albright syndrome is a triad consisting of hyperfunctioning endocrinopathies, irregular (coast of Maine) café-au-lait lesions on the skin, and polyostotic fibrous dysplasia, but only two of these are necessary to make the diagnosis. In girls, breast development and vaginal bleeding occur with sporadic increases in estradiol from autonomously functioning ovarian cysts. Serum gonadotropin levels are low, and GnRH testing elicits a prepubertal response. With time, however, increased estradiol may cause maturation of the hypothalamus, thus leading to true central GnRH-dependent precocity. The syndrome can be associated with other endocrine dysfunctions, including hyperthyroidism, growth hormone excess, and hypercortisolism. In affected tissues, there is an activating mutation in the gene that encodes the alpha-subunit of Gs, the G-protein that stimulates adenylate cyclase. Endocrine cells with this mutation have autonomous hyperfunction and may secrete excess amounts of their respective hormones.

Girls with precocious puberty due to McCune-Albright syndrome are generally treated with an aromatase inhibitor to inhibit the conversion of testosterone to estrogen; or second-line therapy includes estrogen receptor antagonists. In boys, treatment consists of a combination of an aromatase inhibitor and an antiandrogen. For both sexes, if central puberty has been induced, GnRH agonists may also be part of the treatment plan. Because of other manifestations that can occur in this condition, routine screening is required throughout childhood.

18. What is testotoxicosis, and how is it treated?

Familial testotoxicosis is a male-limited autosomal dominant, gonadotropin-independent form of male precocious puberty. Boys with this condition begin to develop true precocity with bilateral testicular and phallic enlargement and growth acceleration by age 4 years. Serum testosterone concentrations are high, but serum gonadotropins are low, and GnRH stimulation shows a prepubertal response. By mid-adolescence to adulthood, GnRH stimulation demonstrates a more typical LH-predominant pubertal response. This condition is caused by an activating mutation in the gene encoding the LH receptor. The mutant LH receptors in the testes are constitutively overactive and do not require LH binding for their activity, resulting in autonomous testosterone production. Because Leydig cells are a minority of cells in the testes, testicular size is only modestly enlarged. Treatment options are the same as for boys with McCune-Albright syndrome. If CPP has been induced, GnRH agonists may also be part of the treatment plan.

19. What is nonclassic CAH, and how is it treated?

CAH is usually caused by genetic mutations in the *CYP21A2* gene, resulting in 21-hydroxylase deficiency, which prevents the normal production of glucocorticoids by the adrenal glands. Because of the underproduction of these hormones, ACTH is elevated, driving the adrenal production of androgens. In classic CAH, there is no functional enzyme, so the presentation is more severe with virilization of female fetuses and salt-losing crises within the first weeks of life in both sexes. In nonclassic CAH, there is a partial function of the enzyme so the presentation is milder, often without signs of adrenal insufficiency. These children may present with premature adrenarche, tall stature, and skeletal advancement. Genetic testing can be considered, particularly if it would change management.

Nonclassic CAH can be treated with glucocorticoids to reduce pituitary ACTH secretion and thereby decrease the overproduction of adrenal hormones. However, this treatment causes iatrogenic adrenal insufficiency, and therefore the risks and benefits of this treatment need to be weighed on an individual basis.

20. What is the association between hypothyroidism and precocity?

Rarely, severe primary hypothyroidism may cause breast development in girls and increased testicular size in boys. This is often called *Van Wyk and Grumbach syndrome.* The exact mechanism is unclear, but one theory is that thyroid-stimulating hormone (TSH), which is elevated in primary hypothyroidism, can stimulate the FSH receptor on the gonads. These children generally present with growth deceleration, as typically seen in hypothyroidism, rather than growth acceleration, as typically seen in precocious puberty. Bone age is usually delayed. Thyroid hormone replacement results in regression of pubertal changes, and no other therapy is necessary.

21. When can early puberty signs be benign?

Isolated thelarche or adrenarche that occurs early but fails to progress through all pubertal stages can be variants of normal puberty. In these benign conditions, pubertal development is usually isolated (i.e., just thelarche or just adrenarche) and often does not progress beyond Tanner stage II–III. There is usually no significant growth acceleration or bone age advancement. An assessment needs to reasonably exclude pathologic and progressive forms of precocious puberty before determining whether the pattern is a benign process.

22. What is benign premature thelarche, and how is it managed?

Benign premature thelarche is defined as isolated breast development in girls without other signs of puberty. Benign premature thelarche is most common in girls who are either under 2 years or between ages 6 and 8 years. Girls with benign premature thelarche may have a history of slowly progressing breast development or waxing and waning breast size. GnRH stimulation may provoke an FSH-predominant response, as opposed to the typical LH-predominant response seen in true central puberty.

The natural course of benign premature thelarche is for the breast tissue to regress or fail to progress. Because of its benign nature, treatment is not necessary except for reassurance and follow-up. Follow-up is critical because premature thelarche may be the first sign of CPP. Measurement of breast tissue diameter during the clinic visit can be helpful for comparison at a later visit.

23. What is benign premature adrenarche, and how is it treated?

Benign premature adrenarche, which occurs in both sexes, is defined as the early development of pubic hair (premature pubarche) and/or axillary hair, body odor, or acne (isolated adrenarche). There are no signs of gonadarche—girls have no breast development and boys have no testicular enlargement. Benign premature adrenarche is caused by early secretion of the adrenal androgens, primarily DHEA-S, and measurement of these hormones correspond to the Tanner stage of development (usually Tanner stage II–III). Benign premature adrenarche occurs more frequently in females and children with exogenous obesity.

The natural course of benign premature adrenarche is slow progression and no to little bone age advancement; however, more exaggerated premature adrenarche in girls has been shown to lead to a slightly earlier onset of central puberty. Girls with premature adrenarche appear to have an increased risk of developing polycystic ovarian syndrome.

24. What is physiologic gynecomastia in puberty? When and how should it be treated?

Typically developing boys often have either unilateral or bilateral breast enlargement during puberty. Breast development generally starts mid-puberty and resolves within 2 years, likely as a result of a transient imbalance of estradiol and testosterone. Pubertal gynecomastia is common and benign and usually only requires reassurance. However, a thorough history and physical examination should be done to evaluate for pathologic causes of gynecomastia, including hypogonadism, rare malignancies, medications, drug abuse, and exposure to lavender or tea tree oils, particularly if gynecomastia occurs prepubertally or beyond Tanner 4.

Pharmacologic treatment with antiestrogens (tamoxifen) or aromatase inhibitors has been used to treat gynecomastia, with mixed results. If resolution of gynecomastia does not occur or if the breast enlargement is excessive, surgery may be considered but should be deferred until puberty is complete.

25. What is delayed puberty?

Delayed puberty is the absence of breast development by age 13 years in girls or testicular volume less than 4 mL by age 14 years in boys. An abnormality in the pubertal axis may also present as a lack of normal pubertal progression, which should be considered if more than 4–5 years have elapsed from the onset of puberty in either sex. Failure to achieve menarche by age 15–16 years or within 3 years after thelarche is considered primary amenorrhea.

26. What features are present in the history of an adolescent with pubertal delay?

The history should include questions regarding the presence of chronic illnesses, autoimmune disorders, nutritional disorders, excessive exercise, galactorrhea, sense of smell, medications, family history of infertility, and timing of puberty in parents and siblings. Weight gain or loss should also be noted.

27. What features are seen in the physical examination of an adolescent with pubertal delay?

Physical examination should include measurement of arm span and upper-to-lower segment ratio. Signs of any chronic illness, malnutrition, anorexia, hypothyroidism, glucocorticoid excess, or features of Turner syndrome or Klinefelter syndrome should be noted. A careful examination should be made for any signs of puberty, such as pubic hair, axillary hair, acne, testicular size (boys), penile length (boys), or breast development (girls). In addition, visual fields and olfaction should be evaluated. The growth chart should be analyzed to evaluate for short or tall stature relative to parental heights and to assess linear growth.

28. How are radiographic studies and gonadotropin levels helpful in the diagnosis of pubertal delay?

Assessment of bone age is critical in determining biological age and the time of expected pubertal development. If linear growth is normal and bone age is less than the normal age for pubertal onset, the diagnosis is likely a constitutional growth delay. If linear growth is impaired and bone age is delayed, it may be necessary to evaluate growth hormone or thyroid function. If bone age has advanced beyond the age for normal puberty, gonadotropin levels are helpful to distinguish between gonadotropin deficiency and primary gonadal failure.

29. What other laboratory tests may be needed?

Additional laboratory studies may include a chemistry panel, complete blood count (CBC), celiac testing, thyroid function tests, estradiol (girls), testosterone (boys), and prolactin levels. If gonadotropins are elevated, chromosome analysis is indicated for both sexes. In the case of low gonadotropins, olfactory testing, and cranial MRI with views of the pituitary gland and olfactory sulci and bulbs are recommended.

30. What is constitutional growth delay, and how does it affect puberty?

Constitutional growth delay is the most common cause of delayed puberty. Children with this growth pattern generally have slower linear growth velocity within the first 2 years of life. After this, growth returns to normal, but along a lower growth trajectory than would be expected for parental heights. Skeletal maturation is also delayed, and the onset of puberty is commensurate with bone age rather than chronologic age. For example, a 14-year-old boy with bone age of 11 years will start puberty when his bone age is closer to 11.5–12 years. This delay in puberty postpones the pubertal growth spurt and closure of growth plates, so that the child continues to grow after his or her peers have reached their final adult height. A key feature of this growth pattern is normal linear growth after 2 years of age. There is often a family history of “late bloomers.”

31. How do you evaluate a girl with primary amenorrhea?

To sort out the many causes of amenorrhea, it is helpful to distinguish if estrogen is sufficient by performing a progesterone challenge. Girls who are producing estrogen will have a withdrawal bleed after 5–10 days of oral progesterone, whereas those who are estrogen deficient will have very little or no bleeding. Those who do not have bleeding should be evaluated for hypogonadism. There are, however, two situations in which girls who have sufficient estrogen will not have a withdrawal bleed: obstruction of the cervix or absence of the cervix or the uterus. In Rokitansky syndrome, maldevelopment of the Müllerian structures leads to an absent or hypoplastic uterus or cervix (or both). Complete androgen insensitivity syndrome in a genetic male results in a phenotypic female who has normal breast development due to the aromatization of testosterone to estrogen. The production of antiMüllerian hormone in males with androgen insensitivity syndrome leads to regression of the Müllerian structures, and thus the absence of a uterus. The absence of a cervix is found in both Rokitansky syndrome and complete androgen insensitivity syndrome. Consequently, a pelvic examination should be considered in all girls who present with primary amenorrhea. (See also Chapter 53.)

32. When is hypogonadism diagnosed?

Functional or permanent hypogonadism should be considered when there are no signs of puberty and bone age has advanced beyond the normal ages for puberty to start. Eunuchoid body habitus is often evident in children with abnormally delayed puberty—a decreased upper-to-lower body ratio and long arm span characterize this habitus. As a rule, serum gonadotropin levels are measured first to determine whether there is hypogonadotropic hypogonadism (gonadotropin deficiency) or hypergonadotropic hypogonadism (primary gonadal insufficiency). If a child's bone age is below the normal age for puberty to start, gonadotropin levels are not necessarily a reliable means of making this diagnosis.

33. What are the causes of hypogonadotropic hypogonadism?

Normal or suppressed gonadotropins indicate failure of the pituitary to stimulate gonadal steroid production. Chronic illness, excessive exercise, malnutrition, anorexia, and depression can cause a functional deficiency of gonadotropins; however, it is reversed when the underlying condition improves. Hyperprolactinemia can cause hypogonadotropic hypogonadism, and only in 50% of cases there is a history of galactorrhea. Other endocrinopathies, such as diabetes mellitus, glucocorticoid excess, and hypothyroidism, can cause hypogonadotropic hypogonadism when these conditions are uncontrolled. Drug abuse, particularly opiates, has been associated with hypogonadotropic hypogonadism. Permanent gonadotropin deficiency is suspected if these conditions are ruled out and gonadotropin levels are low. Gonadotropin deficiency may be associated with other pituitary deficiencies from such conditions as septo-optic dysplasia; tumors, such as craniopharyngioma; trauma; empty sella syndrome; pituitary dysgenesis; Rathke's pouch cysts; or cranial irradiation. Various syndromes, such as Kallmann syndrome, Laurence-Moon-Bardet-Biedl syndrome, and Prader-Willi syndrome, are also associated with gonadotropin deficiency, so genetic testing may be considered, depending on the phenotype. Isolated gonadotropin deficiency (i.e., occurring without another pituitary deficiency) is often difficult to diagnose because hormonal tests do not distinguish with certainty whether a child can produce enough gonadotropins or whether puberty is very delayed. If gonadotropin deficiency cannot be clearly distinguished from delayed puberty, a short course of sex steroids can be given. Patients with constitutional delay often enter puberty after such an intervention. If spontaneous puberty does not occur, the diagnosis of gonadotropin deficiency may be made.

34. What is Kallmann syndrome?

Kallmann syndrome is caused by the abnormal development and/or migration of the GnRH and olfactory neurons, which leads to idiopathic hypogonadotropic hypogonadism with reduced sense of smell (hyposmia or anosmia). On MRI, this can be appreciated through the presence of hypoplastic or aplastic olfactory bulbs. Undescended testes, micropenis, and gynecomastia are common in boys with Kallmann syndrome. Other features that can be seen in Kallmann syndrome include cleft lip/cleft palate, congenital deafness, color blindness, renal anomalies, and certain neurologic differences.

35. What are the causes of hypergonadotropic hypogonadism?

Elevated gonadotropin levels indicate that there is an insufficiency of the gonads to produce enough sex steroids to suppress the hypothalamic–pituitary axis. If hypergonadotropic hypogonadism is diagnosed, a karyotype should be performed. Potential etiologies include:

- Variants of ovarian or testicular dysgenesis—Turner syndrome, Klinefelter syndrome, pure XX or XY gonadal dysgenesis
- Gonadal toxins—chemotherapy (particularly alkylating agents), radiation treatment
- Androgen enzymatic defects—17-alpha-hydroxylase deficiency in the genetic male or female, 17-ketosteroid reductase deficiency in the genetic male
- Complete or partial androgen insensitivity syndrome (mutation in the androgen receptor gene) in genetic males
- Galactosemia; fragile X premutation (in girls only)
- Other miscellaneous disorders—infections, gonadal autoimmunity, vanishing testes, trauma, torsion

36. What is Klinefelter syndrome?

Klinefelter syndrome is the most common cause of testicular failure and results from at least one extra X chromosome. The most common karyotype, 47,XXY, occurs in approximately 1:650 male births. Associated physical features include tall stature, long extremities, small testes, and gynecomastia. Developmental delays and learning disabilities are common. Boys with Klinefelter syndrome will have spontaneous pubertal onset but may fail to progress completely through puberty. Gonadotropins rise out of the normal range within a couple years of pubertal onset, and testosterone often plateaus or even declines rather than sustaining adult concentrations. Testosterone supplementation is indicated in many boys over time to support normal secondary sex characteristics, metabolism, and bone health. Germ cells are decreased in number from birth; Sertoli and Leydig cells are affected to a lesser degree. Men with Klinefelter syndrome are usually azoospermic and infertile; however, advanced reproductive techniques, such as microdissection testicular sperm extraction (mTESE) can now help achieve successful sperm extraction in up to half of young men with Klinefelter syndrome.

37. What is Turner syndrome?

Any consideration of pubertal delay and/or amenorrhea in girls must include the possibility of Turner syndrome. Turner syndrome is characterized by an absent or structurally abnormal second X chromosome. Turner syndrome occurs in approximately 1:2,500 live female births. Girls with Turner syndrome often have short stature and dysmorphic features and are at a higher risk of congenital and acquired heart disease, renal anomalies, frequent otitis media and hearing loss, autoimmunity, and math learning disability. See Table 49.2 for additional clinical findings associated with Turner syndrome.

In the absence of a second functional X chromosome, oocyte degeneration is accelerated, often leaving fibrotic streaks in place of normal ovaries. Because of primary gonadal insufficiency, serum gonadotropin levels rise and are elevated in infancy and again after reactivation of the HPG axis. Approximately 10–20% of girls with Turner syndrome have some ovarian function at puberty that promotes spontaneous breast development. A small percentage of this group will have spontaneous menarche, and an even smaller percentage have fertility potential.

TABLE 49.2 Causes of Precocious Puberty

Central (GnRH Dependent)

- Idiopathic true precocious puberty
- CNS tumors (hamartomas, hypothalamic tumors)
- CNS disorders (meningitis, encephalitis, hydrocephalus, trauma, abscesses, cysts, granulomas, radiation therapy)

Peripheral (GnRH Independent)

Males

- hCG-secreting tumors (CNS, liver)
- CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
- Adrenal tumors
- Leydig cell testicular tumors
- Familial gonadotropin-independent Leydig cell maturation (testotoxicosis)
- Exogenous sex steroids
- McCune-Albright syndrome (polyostotic fibrous dysplasia)

Females

- Follicular cysts
- Ovarian tumors
- Adrenal tumors
- CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
- Exogenous sex steroids
- McCune-Albright syndrome (polyostotic fibrous dysplasia)

CAH, Congenital adrenal hyperplasia; CNS, central nervous system; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

38. How is Turner syndrome treated?

Most girls with Turner syndrome require exogenous estrogen replacement. Low-dose unopposed estradiol, followed by estrogen and progestin, allows the development of secondary sex characteristics. The timing for initiation of estrogen therapy is critical and should be decided by an endocrinologist through discussions with each patient and family. This decision depends on several factors, including height and psychosocial factors. In girls with Turner syndrome, short stature can be treated with growth hormone, with taller final adult height outcomes achieved when growth hormone treatment is started at a younger age. Turner syndrome is ideally managed by an interdisciplinary care team to address the many medical and neurodevelopmental differences that girls with Turner syndrome may experience.

39. How is delayed puberty managed?

The treatment of delayed puberty depends on the underlying cause. If the delayed pubertal development is secondary to anorexia, excessive exercise, hypothyroidism, or illness, treatment of these underlying conditions results in the spontaneous onset of puberty. Puberty also begins spontaneously, albeit late, in constitutional growth delay so that reassurance alone to the patient and family may be sufficient. In some patients with constitutional growth delay, treatment to induce puberty may be appropriate. For boys, a 4- to 6-month course of low-dose depot testosterone (50–100 mg intramuscularly every 4 weeks) can be offered if the bone age is at least 11–12 years. This treatment results in some virilization without adversely affecting final adult height. Spontaneous puberty often begins, as evident by testicular enlargement, 3–6 months after the end of the testosterone course. For girls, a 3-month course of low-dose estradiol (0.25–0.5 mg orally every day) can be offered if the bone age is at least 10–11 years. Therapy is then stopped and physical changes are evaluated. Withdrawal bleeding is unusual after one course of estrogen therapy but may occur with subsequent courses.

40. Why should hypogonadism be treated and when should it be started?

If puberty has not yet started or is not yet complete (Tanner stage 4 or less), hormone replacement is needed for pubertal induction/completion. Following pubertal completion, replacement of gonadal steroids in both sexes is necessary for normal bone mineralization and to prevent osteoporosis, as well as heart health. The timing of starting sex steroid treatment will depend somewhat on the cause of hypogonadism but should ideally begin during the typical timing of puberty or as soon as discovered; however, this may need to be balanced if short stature is also present and growth hormone will be utilized.

41. What is the treatment of hypogonadism in boys?

Most commonly, testosterone esters (enanthate or cypionate) are given intramuscularly or subcutaneously for pubertal initiation, with gradual dose increases to mimic the rise in testosterone during normal puberty over several years. The adult maintenance dose is 200–400 mg per month divided into weekly or biweekly dosing. Other testosterone formulations, including transdermal gel, oral, and buccal formulations require daily or more frequent administration and are more difficult to titrate to precise dosing.

42. What is the treatment for hypogonadism in girls?

Estrogen replacement therapy in hypogonadal girls is begun with very low-dose unopposed estrogen treatment for 12–18 months. Estrogen can be given via an oral tablet or via a transdermal patch, the latter of which is felt to be more physiologic. The dosage used varies depending on height projections and individual response. After this period of unopposed estrogen, cyclic or daily progesterone is added. Progesterone therapy is necessary to counteract the effects of estrogen on the uterus; unopposed estrogen can cause endometrial hyperplasia and increase the risk of carcinoma.

KEY POINTS

Disorders of Puberty

- Central precocious puberty occurs more frequently in girls than in boys. Boys with central precocity, however, have a much higher incidence of underlying central nervous system pathology.
- Precocious puberty must be distinguished from normal variants of early development, such as benign premature thelarche and benign premature adrenarche.
- The most useful diagnostic test to evaluate precocious puberty is a gonadotropin-releasing hormone stimulation test.
- Children with delayed puberty and normal linear growth will most likely have constitutional growth delay.
- Bone age assessment is the first step in evaluating a child with delayed puberty.
- After it has been determined that a child has abnormally delayed puberty, gonadotropins should be measured. If gonadotropins are elevated, chromosome analysis is generally the next step.

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CHAPTER 50

Male Hypogonadism

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1. What is male hypogonadism?

Male hypogonadism is the clinical and biochemical abnormality resulting from the failure of proper functioning of the hypothalamic–pituitary–gonadal (HPG) axis. Normal testes have two functions: (1) synthesis and secretion of testosterone from the Leydig cells and (2) production of sperm from the seminiferous tubules. Testicular disorders causing deficiency of one and/or both functions lead to primary hypogonadism and/or infertility. When a disorder affects the hypothalamus/pituitary, it results in secondary or central hypogonadism due to a lack of appropriate stimulation of gonadotropins (follicle-stimulating hormone/luteinizing hormone [FSH/LH]) on the testes. Depending on the stage of development, hypogonadism may have varied manifestations.

2. What are the manifestations of *in utero* hypogonadism?

In utero androgen deficiency in a genetic male leads to a female phenotype or ambiguous genitalia (male pseudohermaphroditism). The most common cause is a block in the production of testosterone due to congenital testosterone biosynthetic enzyme defects. Rarely, peripheral tissues cannot respond normally to testosterone, resulting in the androgen insensitivity syndromes of testicular feminization (complete) and Reifenstein's syndrome (incomplete). Other manifestations include microphallus, hypospadias, and cryptorchidism.

3. What are the manifestations of peripubertal hypogonadism?

Childhood androgen deficiency results in delayed, incomplete, or absent pubertal development. Common manifestations include:

- Eunuchoid proportions (ratio of pubis-to-vertex/pubis-to-floor is <0.9 and/or arm span is >5 cm more than height). This phenotype is due to the delayed closure of the epiphyses.
- Small testes (<20 ml or <4.5 cm x 3.0 cm)
- Decreased body hair, scant pubic and axillary hair
- Gynecomastia
- Reduced peak bone mass
- Reduced male musculature
- Persistently higher-pitched voice

4. What are the manifestations of hypogonadism in early adulthood?

In early adulthood, an absence/decrease in sperm output (azoospermia/oligospermia) without deficient production of testosterone is common and results in male infertility; thus, infertility is a form of male hypogonadism. A decrease in the production of testosterone in adulthood is usually accompanied by a decline in the production of sperm. When it is not, the term "fertile eunuch" is used (eunuchoid proportions, low levels of LH, low levels of testosterone, normal levels of FSH, and spermatogenesis). Libido and/or potency may be diminished.

5. What are the manifestations of hypogonadism in mid-to-late adulthood?

The most frequent circumstance in which adult hypogonadism occurs is in the middle-aged or senescent man with decreased libido or potency. Semen analysis is rarely performed in these men, since they are usually not concerned with fertility. Other findings may include osteoporosis, diminished androgen production, small prostate, increased fatigue, depressed mood, diminished muscle mass/strength, decreased physical performance, loss of body hair, decreased frequency of shaving, and gynecomastia. If the onset of hypogonadism is acute, the patient may experience hot flashes and sweats.

6. How is the production of testosterone normally regulated?

LH is episodically secreted from the anterior pituitary in response to pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus, thus stimulating the production of testosterone by Leydig cells. Once testosterone is secreted into the bloodstream, it is bound by sex hormone–binding globulin (SHBG) and albumin. The non-SHBG-bound (or "free") testosterone provides negative feedback to the hypothalamic–pituitary unit and thus inhibits the output of LH. This classic endocrine feedback loop serves to maintain serum testosterone at a predetermined level; if serum testosterone falls below the set point, the pituitary is stimulated to secrete LH, which, in turn, stimulates testicular output of testosterone until serum levels return to the set point. Conversely, if serum testosterone rises above the set point, decreased output of LH results in a diminished testicular output of testosterone until serum levels have declined to the set point.

7. How is sperm production normally regulated?

The regulation of sperm production is complex and less clearly understood than the regulation of testosterone production. Both hormonal and nonhormonal factors are important. The Sertoli cells within the seminiferous tubules seem to play an important coordinating role. Sertoli cells respond to FSH by secreting inhibin, androgen-binding protein, transferrin, and other proteins into the blood and/or the seminiferous tubular lumen. Inhibin inhibits the output of FSH from the pituitary gland, thus completing a feedback loop. In theory, if spermatogenesis declines, production of inhibin also should decline; thus, the negative feedback effect on the pituitary would be reduced, leading to an increased output of FSH, which would then stimulate spermatogenesis. However, not all aspects of this feedback loop (FSH–inhibin–spermatogenesis) have been verified experimentally. Moreover, spermatogenesis depends on intratesticular production of testosterone mediated by androgen receptors within Sertoli cells. Initiation of spermatogenesis during puberty requires both LH and FSH. However, reinitiation of the process if it is disrupted by exogenous factors (see the following) requires only LH (or human chorionic gonadotropin [hCG]), although FSH may be needed to produce a normal number of sperm.

8. What is the difference between primary and secondary hypogonadism?

Failure of testicular function may result from a defect either at the testes or the hypothalamic–pituitary level. Testicular disorders leading to hypogonadism are termed primary hypogonadism (Fig. 50.1) or *hypergonadotropic hypogonadism*. Disorders of hypothalamic–pituitary function leading to hypogonadism are termed secondary (central) hypogonadism (Fig. 50.2) or *hypogonadotropic hypogonadism*. This distinction has therapeutic implications. In men with secondary (central) hypogonadism, fertility can generally be restored with appropriate hormonal treatment. Men with primary hypogonadism have fewer options and more limited success with improvement in fertility. The diagnostic evaluation of secondary hypogonadism can reveal a pituitary mass or systemic illness as the underlying cause.

9. What is the initial laboratory workup for hypogonadism?

Primary hypogonadism resulting from a testicular disorder leads to a decline in the production of testosterone and sperm, a consequent decrease in the negative feedback effects on the pituitary, and a corresponding increase in serum levels of LH and FSH. Conversely, in secondary hypogonadism due to a hypothalamic–pituitary disorder, serum LH and FSH may be subnormal or "inappropriately" normal (explainable, in part, by decreased bioactivity) despite low testosterone. A subnormal sperm count and normal testosterone level with a normal LH and elevated FSH suggest primary hypogonadism with a dysfunction of the seminiferous tubules and sperm production but intact Leydig cell function. An algorithm for the logical evaluation of hypogonadism is shown in Fig. 50.3.

10. How are serum testosterone levels measured?

While most automated total testosterone assays are reliable and generally able to distinguish hypogonadism from eugonadism in men, abnormalities in the SHBG level may give falsely low or high total testosterone levels. Due to interassay and interlaboratory variability, total testosterone levels should be measured using an assay verified by an accuracy-based external quality control program.

Equilibrium dialysis is the gold standard for measuring free testosterone but is not commonly available and should only be done by a reliable reference laboratory. Liquid chromatography/mass spectrometry or gas chromatography/mass spectrometry is being used by some reference laboratories to measure testosterone. These are very accurate but expensive methodologies. Analog methods for determining free testosterone are more widely available but are not accurate in the low ranges.

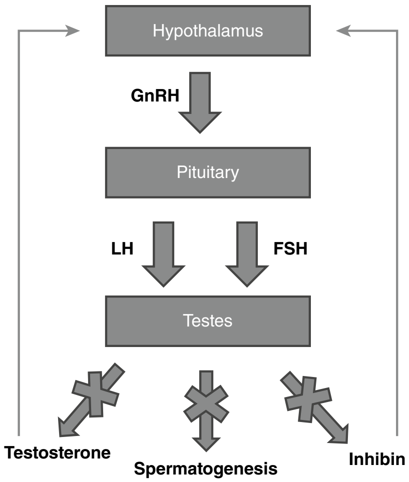

Fig. 50.1 Primary hypogonadism.

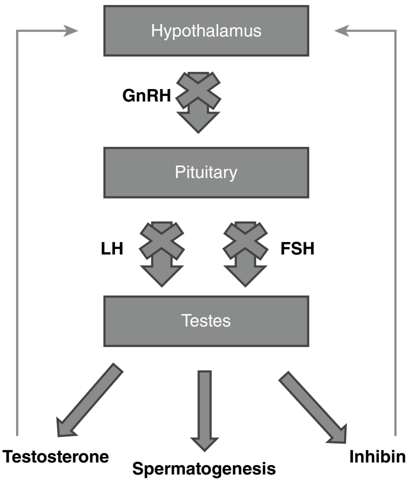

Fig. 50.2 Secondary hypogonadism.

11. What are some conditions associated with decreased or increased serum SHBG levels?

Increase SHBG levels → High total serum testosterone level	***Decrease SHBG levels → low total serum testosterone level***
• Aging	• Obesity
• HIV Disease	• Diabetes Mellitus
• Cirrhosis and hepatitis	• Nephrotic syndrome
• Hyperthyroidism	• Hypothyroidism
• Anticonvulsant use	• Acromegaly
• Estrogen use or herbal preparations for “prostate health” that contain plant-derived estrogens	• Medications (notably glucocorticoids, some progestins, and androgenic steroids)
• Polymorphisms in the SHBG gene	• Polymorphisms in the SHBG gene

12. List the congenital causes of primary hypogonadism

- Klinefelter’s syndrome (47XXY and mosaics)
- Microdeletions of azoospermia factor (AZF) regions of Yp telomere (15% of men with nonobstructive azoospermia; 5–10% of those with oligospermia)
- Bilateral congenital anorchia
- Cryptorchidism
- Myotonic dystrophy
- 5-α reductase deficiency
- 47 XYY syndrome (supermales)
- Polyglandular autoimmune deficiency syndrome
- Congenital adrenal hyperplasia (combined primary and secondary hypogonadism)
- Androgen receptor gene mutation (qualitative or quantitative)
- LH receptor mutations (male phenotype, if mild; female phenotype, if severe)
- Varicocele

13. List the acquired causes of primary hypogonadism

- Cancer therapy: chemotherapy (alkylating agents >cisplatin and carboplatin) and radiation therapy (may be permanent with external radiation; usually transient with radioactive iodine)
- Drugs (e.g., ketoconazole, 5α-reductase inhibitors)
- Testicular trauma or torsion
- Infiltrative disease (e.g., hemochromatosis)
- Infections (e.g., HIV [may be multifactorial], mumps orchitis)
- Orchiectomy
- Systemic illness (e.g., uremia, cirrhosis): maybe multifactorial

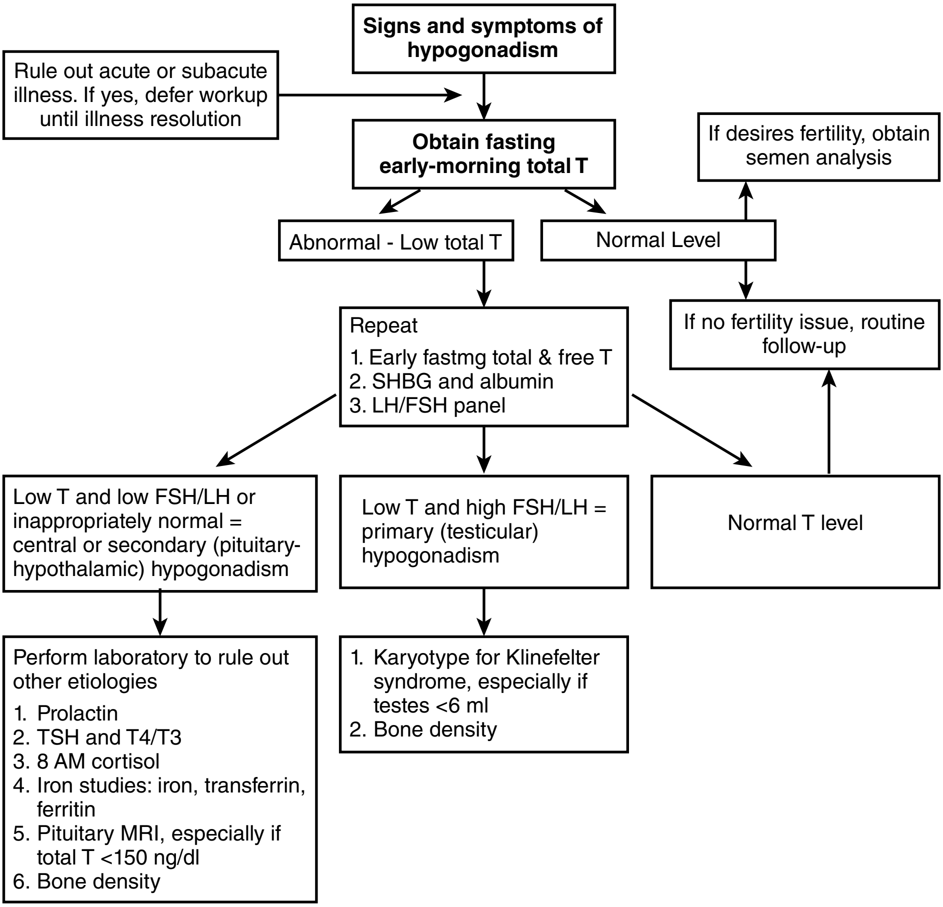
Signs and symptoms of hypogonadism
Rule out acute or subacute illness. If yes, defer workup until illness resolution
Obtain fasting early-morning total T
If desires fertility, obtain semen analysis
Abnormal - Low total T
Normal Level
Repeat
1. Early fastmg total & free T
2. SHBG and albumin
3. LH/FSH panel
If no fertility issue, routine follow-up
Low T and low FSH/LH or inappropriately normal = central or secondary (pituitary-hypothalamic) hypogonadism
Low T and high FSH/LH = primary (testicular) hypogonadism
Normal T level
Perform laboratory to rule out other etiologies
1. Prolactin
2. TSH and T4/T3
3. 8 AM cortisol
4. Iron studies: iron, transferrin, ferritin
5. Pituitary MRI, especially if total T <150 ng/dl
6. Bone density
1. Karyotype for Klinefelter syndrome, especially if testes <6 ml
2. Bone density

Fig. 50.3 Algorithm for the evaluation of hypogonadism. *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *MRI*, magnetic resonance imaging; *SHBG*, sex hormone–binding globulin; *T*, testosterone; *TSH*, thyroid-stimulating hormone.

14. Is normal aging associated with primary hypogonadism?

Symptomatic hypogonadism, defined by at least three signs/symptoms of testosterone deficiency with unequivocally low total testosterone (below assay reference range) and/or low free testosterone (below assay reference range), is present in about 2% of men between 40 and 79 years of age. Using only biochemical criteria, the prevalence is higher (2–6%) in the same age range and 18–40% in men over 70. Not all biochemical hypogonadism is symptomatic. Studies have demonstrated an average 1–2% per year decline in total serum testosterone and an even greater reduction in free testosterone (because of age-related increases in SHBG) associated with normal aging. An increased prevalence of biochemical primary hypogonadism is noted starting at the age of approximately 65–70 due to progressive Leydig cell dysfunction resulting in low testosterone levels with elevated LH. Importantly, comorbidities such as obesity, diabetes, and cancer should be considered when evaluating individual testosterone levels in the elderly male population.

15. What are the causes of secondary hypogonadism?

Any disease that affects the hypothalamic–pituitary axis can cause secondary hypogonadism. Involvement of the hypothalamus or pituitary stalk interferes with the secretion of GnRH or the ability of GnRH to communicate with the pituitary. Various anatomic lesions of the pituitary cause secondary hypogonadism by interfering with the release of LH and FSH. Such lesions include benign tumors and cysts, malignant tumors (both primary central nervous system tumors and metastatic tumors from distant sources), vascular aneurysms, infiltrative diseases (e.g., hemochromatosis), pituitary hemorrhage, and pituitary trauma. Certain inflammatory diseases (such as sarcoidosis and histiocytosis) can also affect the hypothalamus and pituitary resulting in decreased testosterone production. Congenital disorders, in which the output of LH and FSH is impaired, such as Kallmann syndrome (see below), also lead to secondary hypogonadism. Obesity, sleep disorders, nutritional deficiency, excessive exercise, eating disorders, and HIV/AIDS can be associated with secondary hypogonadism as well. Drugs commonly used in the treatment of benign prostatic hypertrophy, the 5-α reductase inhibitors, finasteride and dutasteride, are among the iatrogenic causes of hypogonadism. Immune checkpoint inhibitors also cause hypopituitarism with resultant secondary hypogonadism. Others include the use of narcotic analgesics, glucocorticoids, alcohol, or the abuse of marijuana or anabolic steroids.

16. What assessment for congenital hypogonadotropic hypogonadism (CHH) should be done?

Kallmann syndrome is a congenital condition characterized by hypogonadotropic hypogonadism affecting puberty (delayed or impaired) and an impaired sense of smell. The sense of smell in the patient (and his relatives) should be assessed by direct questioning. Olfactometry, a quantitative or semiquantitative method, can also be done. In addition, an MRI can be performed to assess the olfactory bulb. If the sense of smell is normal and there does not appear to be a syndromic form of CHH (i.e., Kallmann syndrome), then the most common gene abnormalities are *GNRHR, KISS1R, GnRH1, TAC3,* and *TACR3*. If the sense of smell is decreased or absent in a man with CHH, then the diagnosis is Kallmann syndrome. *KAL1* mutations cause Kallmann syndrome, especially in men with mirror movements (bimanual synkinesis), renal agenesis, and an x-linked pattern of inheritance. *FGFR1* mutations occur more often in patients with Kallmann syndrome and midline abnormalities (e.g., cleft lip/palate, short metacarpals, and/or metatarsals) but can occur in normosmic CHH. *FGF8*, *PROK2*, or *PROKR2* mutations are more common in Kallmann syndrome but can also occur in normosmic CHH.

17. What is the most common pituitary tumor in adults?

The most common pituitary tumor found in adults is a benign prolactin-secreting adenoma. These tumors primarily cause hypogonadism as a result of local destruction and compression of gonadotrophs, thereby inhibiting the production and release of LH and FSH. Elevated prolactin levels can also interrupt the secretion of GnRH, although this is usually of much less significance in men than the mass effect.

18. How do other pituitary adenomas cause hypogonadism?

Pituitary adenomas that produce growth hormone (acromegaly) or adrenocorticotropic hormone (Cushing's disease) and nonfunctioning pituitary tumors may similarly cause secondary hypogonadism by their mass effects.

19. What clinical symptoms and signs are seen in male hypogonadism?

- Specific symptoms and signs of hypogonadism include incomplete or delayed sexual development, loss of body (axillary and pubic) hair, and very small testes (<6 mL)
- Suggestive symptoms and signs include reduced sexual desire (libido) and activity, decreased spontaneous erections, erectile dysfunction, breast discomfort, gynecomastia, eunuchoidal body proportions, height loss, low-trauma fracture, low bone mineral density, hot flashes, episodic sweats.
- Nonspecific symptoms and signs commonly associated with hypogonadism include unexplained normochromic, normocytic anemia, decreased energy and motivation, poor concentration and memory, depressed mood, sleep disturbance, reduced muscle bulk and strength, and increased body fat and body mass index.
- Loss of the sperm-producing function of the testis leads to infertility, usually defined as the failure of a normal female partner to conceive after 12 months of unprotected intercourse.

20. What questions are most helpful in determining if a man may have hypogonadism?

When associated with a low total and/or free testosterone, the following questions are useful in establishing a diagnosis of clinical hypogonadism:

a. How frequently have you awakened with a full erection in the past month?
b. Are you able to get and keep an erection sufficient for sexual intercourse?
c. How often do you think about sex?

21. How does hypogonadism affect bone architecture?

Osteoporosis is now a well-recognized result of both primary and secondary hypogonadism. Trabecular architecture (and bone strength) is even more severely disturbed than bone density in men with hypogonadism. Thus, it is not surprising that hypogonadism is found in up to 30% of men with vertebral fractures. Estradiol, which derives from the aromatization of testosterone, may be the most important factor in preserving bone architecture and density in both men and women. However, androgen receptors are also found in bone and may explain the sexual dimorphism of bone density.

22. What laboratory tests help to confirm a suspected diagnosis of male hypogonadism?

The main functions of the testis, the production of sperm and the production of testosterone, are readily assessed by semen analysis and measurement of serum testosterone, respectively.

A. Normal semen analysis values in men following 2–3 days of abstinence are: 20 million sperm per milliliter and >60% motility of the sperm. Because sperm density is highly variable from day to day in all men, accurate assessment usually involves several semen analyses done with the same abstinence period each time.

B. The best initial test for testosterone production is the measurement of the fasting morning serum total testosterone level. Serum testosterone also varies considerably from moment to moment, in the fasting versus nonfasting state, as glucose and food intake suppress testosterone levels, and from morning to night in response to LH secretion because of diurnal variation; again, several fasting early-morning samples may be needed to establish an accurate measurement. In addition, most testosterone in serum is bound to plasma proteins, particularly SHBG; thus, in patients who have increased or decreased SHBG levels (see above), and in those men in whom plasma protein levels may be disrupted, measurement of the physiologically active "free" testosterone may prove informative. Patients should be advised to stop all performance-enhancing supplements for 3 months or more and stop biotin supplements for 72 hours before testing.

C. Bone density measurement using a dual-energy x-ray absorptiometry (DXA) is used to screen for bone loss/osteoporosis. The results may provide helpful baseline information to assist in deciding whether or not to prescribe androgen replacement therapy. Recent evidence suggests that testosterone not only doesn't reduce fracture rates in elderly men but actually increases them. Bone density measurements were not obtained in that study.

23. What other diagnostic tests are useful in defining the cause of male hypogonadism?

Additional diagnostic testing should be based on clinical suspicion and the results of preliminary testing. For example, in cases of secondary hypogonadism (hypogonadotropic hypogonadism), measurement of serum prolactin and pituitary imaging, preferably MRI with gadolinium, should be done. Computed tomography (CT) of the sella turcica usually detects macroadenomas (>1.0 cm) but will miss many clinically significant microadenomas and is, therefore, less preferable than MRI. Plain x-rays of the skull or sella turcica are not adequate for diagnosis. Measurement of other pituitary hormones also may be appropriate to assess either possible tumoral hypersecretion (e.g., Cushing's disease, acromegaly) or tumor-related panhypopituitarism. Visual field testing is indicated if a pituitary macroadenoma is present or if there is a suprasellar extension. Likewise, the initial findings in primary hypogonadism (hypergonadotropic hypogonadism) may suggest additional tests. For example, small firm testes, gynecomastia, azoospermia, modestly reduced serum testosterone, and high levels of serum LH and FSH in a young man should lead to chromosome analysis to confirm a presumptive diagnosis of Klinefelter's syndrome. Measurement of serum estradiol levels may be helpful when feminization is prominent clinically, as with secondary hypogonadism related to the production of estrogen by testicular or adrenal tumors or surreptitious use by transgender persons. If infertility is the primary issue and no hormonal abnormality is found, genetic causes should be investigated. This includes testing for Y chromosome microdeletion syndromes. Testis biopsy rarely provides information that is useful in establishing a specific diagnosis, prognosis, or treatment. In addition, if an infiltrative process is suspected, ferritin and an iron panel should be ordered to screen for possible hemochromatosis.

24. Define the term *hermaphrodite.*

Hermaphrodite refers to someone who has both ovarian and testicular elements in their body. These individuals usually have a 46XX or 46XX/46XY karyotype. They may have an ovary and a testis or an ovotestis. They most often have ambiguous genitalia. Hermaphrodite is now a disfavored term used for individuals who have both male and female gonads.

TABLE 50.1 Testosterone Treatment Options in the United States

FORMULATION	REGIMEN	ADVANTAGES	DISADVANTAGES
Parenteral			
Testosterone enanthate or cypionate in oil	50–100 mg IM per week or 50–400 mg IM every 2–4 weeks (deep SC may be preferable route of administration)	Relatively inexpensive; flexibility of dosing	IM injection resulting in supra-physiologic serum T levels which then decline into the hypogonadal range; "peak" and "trough" fluctuation can cause emotional lability and "let-down" effect
Testosterone undecanoate	750 mg initially, followed by 750 mg after four weeks, followed by 750 mg every 10 weeks	Extra-long acting injection	Injection-associated pulmonary oil microembolism (POEM)
Transdermal/Topical			
Testosterone Gel	Apply 20.25–100 mg per pump or packet per day to clean, dry, intact skin but not to genitals	Good skin tolerability; flexibility of dosing; ease of application	Potential of transfer to others by direct skin-to-skin contact; occasion skin irritation; moderately high DHT levels
Testosterone Patch	Apply 2–6 mg daily to clean, dry, intact skin but not to genitals	Ease of application	Frequent skin irritation at the application site
Testosterone Topical Solution	Apply 30 mg/actuation, 1–4 actuations per day to axilla daily	Good skin tolerability; flexibility of dosing; uses an applicator	Potential of transfer to others by direct skin-to-skin contact; occasion skin irritation
Other			
Testosterone Implant Pellets	75 mg pellets, dose150–450 mg subcutaneous implant every 3–6 months	Ensures compliance	Requires surgical incision for insertions; pellets may extrude spontaneously
Testosterone undecanoate	Oral Capsule; 158–225 mg bid depending on brand	Ease of use	Need to ingest twice daily to maintain stable levels
Nasal testosterone gel	11mg bid or tid	Rapid absorption and avoid hepatic first pass metabolism	Local nasal irritation/side effects, not good with nasal disorders, frequent administration

25. Define the term *pseudohermaphrodite.*

Pseudohermaphrodite refers to someone whose external genitalia are not consistent with his or her gonadal sex. A male pseudohermaphrodite, for example, has a 46XY karyotype and testes but has either ambiguous genitalia or a complete female phenotype. Most often, this results from genetic disorders of testosterone biosynthetic enzymes, the androgen receptor, or the 5-α reductase enzyme; the severity of the phenotype depends on the severity of the genetic defect. A female pseudohermaphrodite, in contrast, has a 46XX karyotype and ovaries but has ambiguous external genitalia. The most common cause of this is congenital adrenal hyperplasia, which causes in utero virilization of the female fetus. Pseudohermaphrodite is now a disfavored term for individuals who have atypical genital appearance but do not have both male and female gonads.

26. How do you treat hypogonadism?

Deficiency of testosterone is easily treated with testosterone replacement therapy (TRT) (see Table 50.1). An alternative approach is oral clomiphene citrate, which blocks the feedback of estrogen on the hypothalamic-pituitary axis thereby causing an increase in LH and FSH with a resultant increase in testosterone. In general, the treatment goal for all TRT is the normalization of the serum total testosterone level in the mid-normal range. However, in elderly men, the goal of therapy should be to raise serum testosterone levels to the low-normal range (i.e., 300–400 ng/dL) to reduce the risk of testosterone-dependent diseases. There is currently considerable controversy over whether or not men with age-associated hypogonadism should be treated with TRT. While some short-term studies have demonstrated treatment benefits, long-term large studies are lacking and are needed to clarify the criteria for treatment, as well as the risks and benefits associated with TRT in this population. TRT in older men should be guided by an individualized assessment of risks, benefits, and patient values. In testosterone-deficient men of any age, osteopenia/osteoporosis and/or reduced hematopoiesis may be indications for TRT even in the absence of decreased libido or erectile dysfunction; however, osteoporosis is more effectively and safely treated with osteoporosis medications approved by the US Food and Drug Administration (FDA). Testosterone preparations are presently designated as Schedule III drugs by the *Anabolic Steroid Control Act* because of their potential for abuse by athletes and others.

The formulations of testosterone therapy include oral capsules of testosterone undecanoate, nasal gels, transdermal gels, transdermal patches, transdermal axillary solutions, implant pellets, intramuscular testosterone enanthate or cypionate, and injectable long-acting testosterone undecanoate in oil.

27. What are the potential adverse effects of testosterone treatment?

Gynecomastia and acne are rare symptoms that may occur in the first few months after initiating TRT; these side effects may resolve with continued treatment, although temporary dose reduction may be helpful. Abnormalities in liver function are uncommon with currently used injectable and transdermal preparations. A testosterone-induced increase in hematocrit is common, especially when testosterone injections are used, although clinically significant polycythemia is quite rare unless the drug is being abused. TRT may also precipitate or worsen sleep apnea; marked increases in hematocrit may be a clue to this side effect. Skin reactions are commonly seen in patients using the transdermal patch, and are occasionally, but much less frequently, seen with the use of gels. In boys who have not yet gone through puberty, the rapid increase in serum testosterone after initial treatment may lead to considerable psychological difficulties and physically aggressive behavior; initiating treatment with smaller doses may be helpful. TRT, when titrated to the recommended targets, has no adverse effect on lipid profiles compared with eugonadal men, but overtreatment can lead to several lipid abnormalities, including decreases in the high-density lipoprotein (HDL) cholesterol level. There does not appear to be a significant increase in cardiovascular disease associated with physiologic TRT, and some studies have even suggested a treatment benefit. However, patients with Class III or IV heart failure should be given TRT cautiously. In addition, there is an increase in risk of venous thromboembolism (VTE), especially in the first 6 months after testosterone initiation, as reported in a large population-based case-control study in the United Kingdom. Other concerns include increased detection of subclinical prostate cancer, growth of metastatic prostate cancer, reduced sperm production and fertility, growth of breast cancer, or worsening of obstructive sleep apnea. Possible adverse effects of newly FDA-approved oral testosterone undecanoate include headache, increased hematocrit, upper respiratory infections, hypertension, decreased HDL cholesterol, nausea, rashes, and overdose.

28. Does testosterone replacement affect the prostate in older men?

In older men, the effects of TRT on the prostate must be considered, including the possibility of precipitating urinary retention due to testosterone-induced prostatic hypertrophy. Short-term studies have not shown any histologic or gene expression effects of TRT. In hypogonadal men, prostate volume increases with long-term TRT to a level comparable to eugonadal men without any significant associated increase in symptoms, urine flow rates, or residual volumes. Nonetheless, individual men may experience voiding symptoms associated with this enlargement, and they should be advised to monitor this. It is advisable to perform a digital rectal examination (DRE) of the prostate and monitor prostate-specific antigen (PSA) in middle-aged and older men before and annually while they are receiving any TRT. Although no compelling evidence indicates that TRT causes prostate carcinoma, the potential for testosterone stimulation of occult prostate cancer exists. Men with an elevated PSA level or an abnormal DRE should be evaluated further, potentially including a prostate biopsy, prior to initiation of TRT.

29. How does one treat the deficiency of sperm production in primary hypogonadism?

In men with primary hypogonadism, as manifested by elevated levels of serum FSH, there seems to be no effective pharmacologic treatment for increasing the sperm count. Anatomic lesions, such as varicoceles and ejaculatory duct obstructions, can be corrected surgically, but improvement in spermatogenesis may not result. If one plans to use a medication known to cause hypogonadism (e.g., cancer chemotherapeutic agents), it may be desirable to cryopreserve semen specimens before treatment, provided that treatment is not unduly delayed.

30. How does one treat deficient sperm production in secondary hypogonadism?

The outlook is more optimistic with secondary hypogonadism, particularly if the condition develops after puberty. Treatment with gonadotropins (hCG with or without FSH) may be successful in restoring the production of sperm, as well as testosterone. The pretreatment size of the testes is often a clue to prognosis; a larger testis size is associated with a better outcome. Production of testosterone and sperm in men with secondary hypogonadism also may be enhanced with pulsatile administration of GnRH via a portable infusion pump, provided that the pituitary retains the capability to make gonadotropins. Treatment with gonadotropins or GnRH tends to be both costly and prolonged.

31. What alternative is available to men with hypogonadism who do not respond to therapy with an increase in spermatogenesis?

In men with primary or secondary hypogonadism who have not responded to specific therapy and who have preservation of some germ cells in either ejaculate or testis, assisted reproductive therapies should be considered. Intracytoplasmic sperm injection (ICSI) may offer some hope, although at a high financial cost. The prognosis for successful ICSI is dependent on the site and extent of microdeletions on the Y chromosome. If microdeletions are found, the patient should be counseled about the possibility of transmitting this on to his male child. Microsurgical testicular sperm extraction (micro-TESE) is a surgical method for harvesting sperm. Fertility options that should be discussed also include donor sperm and adoption.

32. What are the advantages and disadvantages of the various forms of androgen replacement therapy?

The available forms of testosterone (T) treatment in the United States are shown in Table 50.1.

33. What parameters should be monitored in men on testosterone therapy?

The following should be determined at baseline, at 3 months after initiation of TRT, and then followed at least yearly, once the patient is stabilized:

- Serum testosterone levels in all forms of TRT (goal serum T level in the mid-normal range)
- Hematocrit and hemoglobin
- Serum prostatic-specific antigen (PSA)
- Liver function tests
- Lipid panel
- Prostate size by DRE (for all patients 55–69 and for patients 40–55 at increased risk for prostate cancer)
- Development of gynecomastia, acne, or edema
- Development, or worsening, of sleep apnea
- Bone mineral density at baseline and at one to two years after treatment for patients with osteoporosis.

34. In what conditions is testosterone therapy absolutely or relatively contraindicated?

Absolute contraindication:

- Prostate cancer
- Untreated and severe obstructive sleep apnea
- Erythrocytosis (hematocrit >50%)
- Severe lower urinary tract symptoms
- Breast carcinoma
- PSA >4 ng/mL

Relative contraindication:

- Prostate nodule that has not been biopsied
- Class III or IV congestive heart failure

KEY POINTS

Male Hypogonadism

- The manifestations of hypogonadism vary depending on the patient's stage of development when the hypogonadism occurs.
- A reduction in testicular volume <20 mL is the most common manifestation of hypogonadism and is seen in nearly all cases of long-standing hypogonadism.
- Classify hypogonadism as primary (a disorder at the level of the testes) or secondary (a disorder at the level of the hypothalamus or pituitary).
- Therapeutic goals are generally to correct testosterone to the mid-normal range topically or by injection.
- Monitor patients on testosterone replacement for polycythemia, sleep apnea, gynecomastia, psychological difficulties, prostate size, prostate symptoms, and increases in PSA levels.

WEBSITES

1. https://www.endocrine.org/patient-engagement/endocrine-library/hypogonadism
2. http://www.nlm.nih.gov/medlineplus/ency/article/000390.htm
3. https://my.clevelandclinic.org/health/diseases/15603-low-testosterone-male-hypogonadism
4. http://www.mayoclinic.com/health/male-hypogonadism/DS00300

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Erectile Dysfunction

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1. What is impotence?

The medically appropriate term for impotence is erectile dysfunction (ED). Classically, ED has been defined as the inability to attain and maintain an erection of sufficient rigidity for sexual intercourse in 50% or more attempts for at least 3 months. This definition is important to consider because any normal male can have occasional ED, and treating men with only occasional symptoms is not without risk.

2. Do men with ED have disturbances in other sexual functions?

Most men with ED are able to ejaculate. Premature ejaculation may precede the development of impotence and is sometimes associated with drug therapy. Sexual desire (libido) is usually preserved; loss of libido is suggestive of hypogonadism or severe systemic or psychiatric illness.

3. Is impotence common?

ED affects approximately 30 million men in the United States and 300 million men worldwide. Another 10 million may suffer from partial ED. The prevalence of ED increases with age; about 2% of 40-year-old, 20% of 55-year-old, and 50–75% of 80-year-old men are impotent. Of interest, there is a libido–potency gap in that many elderly men continue to have active libidos, but only 15% of them engage in sexual activity.

4. How does a normal erection occur?

Erection is primarily a vascular event that results from the complex interplay of the hormonal, vascular, peripheral, and central nervous systems. There is considerable psychological interplay in that underlying psychiatric conditions or medications can cause decreased erectile function. Conversely, undesired sexual symptoms can also adversely affect mood and self-perception.

5. Explain the role of the nervous system in achieving erection.

Erection is usually initiated by various psychological and/or physiologic stimuli in the cerebral cortex. The stimuli are modulated in the limbic system and other areas of the brain, integrated into the hypothalamus, transmitted down the spinal cord, and carried to the penis via both autonomic and sacral spinal nerves. Sensory nerves from the glans of the penis enhance the message and help maintain an erection during sexual activity via a reflex arc.

6. Explain the hormonal aspects of erection.

Nervous system stimuli release neurotransmitters that reverse the tonic smooth muscle constriction maintained by norepinephrine, endothelin, and other vasoconstrictive factors. The most important of these are the potent vasodilators, nitric oxide (NO) and prostaglandin E1 (PGE1). In addition to neural sources, NO is derived from endothelial cells, which may explain why endothelial integrity may be necessary for the maintenance of an erection. NO works by increasing cyclic guanosine monophosphate (cGMP) and causing a decrease in intracellular calcium. This results in the relaxation of vascular smooth muscle cells due to the dissociation of actin-myosin. The role of testosterone in erectile function remains complex and controversial. Testosterone has a critical role in stabilizing intracavernosal NO synthase, and for fully satisfactory sexual function a "normal" quotient of testosterone must be present. Testosterone is also the main hormonal mediator of a male's libido, which means that its deficiency can have a psychological impact on erectile function. Regardless, some men with testosterone levels below the reference limit still have normal erections. Testosterone replacement is therefore not guaranteed to cure ED in hypogonadal men, nor is it indicated in men with normal testosterone levels with impaired sexual function.

7. What vascular changes in the penis result in erection?

Within the two spongy corpora cavernosa of the penis are millions of tiny spaces called lacunae, each lined by a wall of trabecular smooth muscle. As neurotransmitters dilate cavernosal and helicine arteries to the penis and relax the trabecular smooth muscle, the lacunar spaces in the penis become engorged with blood. This results in entrapment of the outflow vasculature between the expanding trabecular walls and the rigid tunica albuginea that surrounds the corpora cavernosa, thereby greatly reducing venous outflow from the penis. This veno-occlusive mechanism accounts for both rigidity and tumescence. Failure of venous occlusion (venous leak) is one of the intractable causes of ED.

8. What types of nerves and neurotransmitters play a role in penile erection?

At least three neuroeffector systems play a role in penile erection. Adrenergic nerves generally inhibit erection; cholinergic nerves and nonadrenergic, noncholinergic (NANC) substances enhance erection as follows:

- Sympathetic nerves (via β-adrenergic receptors): constrict cavernosal and helicine arteries and contract trabecular smooth muscle.
- Parasympathetic nerves (via cholinergic receptors): inhibit adrenergic fibers and stimulate NANC fibers.
- NANC messengers (NO, vasoactive intestinal polypeptide, and PGs or other endothelium-derived factors): dilate cavernosal and helicine arteries, and relax trabecular smooth muscle.

9. How does detumescence occur?

Phosphodiesterase 5 (PDE5) causes a decrease in cGMP, allowing for a reversal of this process, known as detumescence. This makes PDE5 inhibitors, such as sildenafil, vardenafil, tadalafil, and avanafil, important therapeutic agents for the treatment of ED (see Section 23).

10. What are the common causes of ED?

The frequency of the various causes of ED is difficult to assess because of the large number of men who do not report the problem, confusion regarding the diagnosis, and variability in the sophistication of the initial evaluation. Primary causes of ED in men presenting to a medical outpatient clinic are approximated as follows:

- Endocrine factors (hypogonadism, hyperprolactinemia, hyper- and hypothyroidism, hyper/hypocortisolism)
- Vascular–related causes (cardiovascular disease, diabetes mellitus, chronic kidney disease, hypertension, hyperlipidemia, obstructive sleep apnea, smoking, metabolic syndrome, radiotherapy [pelvis or retroperitoneum], surgery [radical prostatectomy])
- Medications (antihypertensives, antidepressants, antipsychotics, antiandrogens, recreational drugs, etc.)
- Systemic disease and alcoholism
- Primary neurologic causes (multiple sclerosis, Alzheimer's disease, Parkinsonism, myotonic dystrophy, spinal cord diseases, stroke, CNS tumors, etc.)
- Structural disease (Peyronie's disease, penile fracture, cavernous fibrosis)
- Psychogenic (stress, anxiety, depression, etc.) or unknown causes

11. What lifestyle factors are associated with ED?

- Sedentary lifestyle
- Obesity
- Smoking
- Alcohol abuse

12. Besides diabetes mellitus, what are the three most common endocrine causes of ED?

- Primary (hypergonadotropic) hypogonadism (increased luteinizing hormone [LH] and decreased testosterone)
- Secondary (hypogonadotropic) hypogonadism ("inappropriately" normal or decreased LH combined with decreased testosterone)
- Hyperprolactinemia

13. Describe the most common drugs known to induce ED.

Nonprescription drugs, such as alcohol, and illicit drugs, such as cocaine, methadone, and heroin, can cause ED. Prescription drugs most commonly associated with ED include the following:

- Antihypertensive agents, especially methyldopa, clonidine, beta blockers, vasodilators (e.g., hydralazine), thiazide diuretics, and spironolactone
- Antiandrogens (gonadotropin-releasing hormone agonists, spironolactone)
- Antipsychotic medications (neuroleptics, etc.)
- Antidepressants and sedatives (SSRIs, SNRIs, TCAs, etc.)
- Others (especially cimetidine, digoxin, phenytoin, carbamazepine, ketoconazole, metoclopramide, and megestrol)

14. Which antihypertensive agents should be used in men with ED?

Virtually every blood pressure medication has been associated with ED. While there is little overall difference in the rate of erectile problems among the commonly prescribed antihypertensive agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and calcium channel blockers are the agents least likely to affect erectile ability. Alpha-adrenergic blockers, such as doxazosin, have been reported to enhance libido and sexual function. When beta blockade is required, selective beta antagonists, such as atenolol or acebutolol, are preferred as they have minimal impact on sexual function.

15. What is “stuttering” impotence? What is its significance?

ED alternating with periods of entirely normal sexual function is termed *stuttering impotence*. Multiple sclerosis (MS) is the most significant organic cause of stuttering impotence. It may be the initial manifestation of MS and may be present in up to 50% of men with the disease.

16. What historical information helps to separate organic from psychogenic ED?

True psychogenic ED is uncommon and should be a diagnosis of exclusion. Questions that may help separate psychogenic from organic ED are listed in Table 51.1. A detailed history assessing for contributing physical/psychiatric conditions can also help with this distinction. These include obesity, hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus or other endocrinopathy, neurologic disease, prior pelvic surgery or irradiation, trauma, Peyronie’s disease, substance abuse, depression, or the aforementioned medications. A detailed social history is also important and includes an assessment of stressors and the patient’s coping mechanisms, concomitant psychosexual problems like premature ejaculation, and relationship dynamics with partner(s). A validated questionnaire such as the International Index of Erectile Function may be used to assess the severity of symptoms and response to therapy.

17. Name the essential components of a physical examination in a man complaining of ED.

- Secondary sexual characteristics such as muscle development, hair pattern, and presence of breast tissue.
- Vascular examination, especially of the femoral and lower extremity pulses and the presence of bruits.

TABLE 51.1 Comparing Organic and Psychogenic ED

	ORGANIC	PSYCHOGENIC
Was ED onset abrupt?	No	Yes
Is ED stress dependent?	No	Yes
Is libido preserved?*	Yes	No
Do you have morning erections?	No	Yes
Do you have orgasms?	Yes	No
Can you masturbate?	No	Yes
Does ED occur with all partners?	Yes	No

ED, erectile dysfunction

*There is a general relationship of libido to hypogonadal levels of testosterone in populations but on an individual basis, libido may not be a reliable discriminator.

- Focused neurologic examination, including assessing the presence of peripheral neuropathy with vibratory and light touch sensation and of autonomic neuropathy using the cremasteric reflex, anal sphincter tone, and/or the bulbocavernosus reflex, evaluation for postural hypotension with standing and supine blood pressure measurement, and measurement of the heart rate response to deep breathing and Valsalva (diabetics rarely have autonomic neuropathy as a cause of ED in the absence of peripheral neuropathy).
- Examination of the genitalia to determine the penile size, shape, presence of plaque or fibrous tissue (Peyronie's disease); size and consistency of the testes (the normal testis size is more than 5 × 3 cm or 20 mL measured using an orchidometer); prostate examination (prostatic enlargement or irregularity/nodularity).
- Thyroid relevant examination including size, the presence of nodularity, and abnormal reflexes.

18. What is the appropriate laboratory assessment for men with ED?

Laboratory assessment should be based on history and physical examination findings. It can discover previously unknown disease in 6% of men. Generally, it should include the following:

- Complete blood count
- Urinalysis
- Fasting plasma glucose and (in known diabetics) hemoglobin A1C (HbA1C)
- Fasting serum lipid profile
- Serum creatinine
- Serum-free thyroxine and thyrotropin
- Serum testosterone (fasting, morning sample), LH, and FSH

19. Should prolactin levels be measured in all men with ED?

Whether serum prolactin should be measured in all men with ED is somewhat controversial. In general, patients with normal levels of testosterone and LH and a normal neurologic examination do not require measurement of prolactin. However, if testosterone is low and associated with low or low-normal LH or if history or examination suggests a pituitary lesion, prolactin should be measured. Because prolactin interferes with the action of testosterone, prolactin status should be assessed in hypogonadal men unresponsive to testosterone replacement therapy. Hypothyroidism and renal failure also may elevate prolactin.

20. What is the role of vascular testing in evaluating ED?

Specialized testing to evaluate ED may include intracavernosal injection testing (ICI) or penile duplex ultrasound (DUS). These tests can indicate if there is a vascular cause for ED that may affect management.

ICI testing evaluates the veno-occlusive function of the penis. Prostaglandin is injected into the corpora cavernosa and erectile response is assessed 5–10 minutes after injection and sexual stimulation. Anxiety or fear related to anticipation of the injection may result in false positives, and repeat testing or alternate testing should be done if this is suspected.

DUS involves an ultrasound of the erect penis and incorporates quantitative data including peak systolic velocity, cavernosal artery blood flow rates, and end-diastolic velocity. DUS is considered the gold standard by the American Urological Association in penile vascular evaluation, since it is minimally invasive and can assess both cavernous arterial inflow and veno-occlusive function of the penis. However, it should only be performed by specialists (generally urologists) who have the training and experience to perform this procedure.

21. What is nocturnal penile tumescence monitoring?

Most men experience three to six erections during the night that are entrained to rapid eye movement (REM) sleep. By monitoring such events, one can assess the frequency, duration, and, with some instruments, even the rigidity of erection. This procedure helps distinguish organic from psychogenic impotence. This can be done at home either semiquantitatively (using a Snap-Gauge) or more quantitatively (using the RigiScan). The nocturnal penile tumescence and rigidity evaluation should be done on at least two nights, with a functional erectile mechanism indicated by an erectile event of at least 60% rigidity recorded at the penile tip that lasts for more than 10 minutes. This test may be less useful in men with impaired sleep schedules.

22. What are the therapeutic options in the treatment of ED?

Once drugs with a high likelihood of causing impotence are discontinued and/or other underlying conditions are aggressively treated (e.g., diabetes mellitus, hypercholesterolemia), the broad categories of available medical and surgical therapy are summarized in Table 51.2. Important adjuncts include:

- Medical treatment including lifestyle modifications and/or weight reduction
- External mechanical aids and vacuum/suction devices
- Psychological therapy (especially in the absence of an obvious organic cause)

23. What options are available for medical treatment?

- Testosterone replacement in hypogonadal men with a goal of achieving a mid-normal level of serum testosterone (see chapter on hypogonadism)
- Dopamine agonists (bromocriptine or cabergoline) to reduce hyperprolactinemia in hypogonadal men unresponsive to testosterone treatment
- PDE5 inhibitors, such as sildenafil citrate (Viagra), vardenafil (Levitra), tadalafil (Cialis), or Avanafil (Stendra) (see Table 51.3)
- Selective serotonin reuptake inhibitors for premature ejaculation
- Eroxon is a newly FDA-approved topical gel that can be obtained without a prescription.

24. How effective are PDE5 inhibitors?

The introduction of the selective PDE5 inhibitors [sildenafil citrate [Viagra], vardenafil [Levitra], tadalafil [Cialis], and avanafil [Stendra]) has produced a paradigm shift in the approach to the treatment of ED by reducing the relevance of finding a specific cause of the problem. There appears to be no tachyphylaxis to their effect for at least 5 years. Given 1 hour before anticipated sexual activity (and, for sildenafil, vardenafil, and avanafil, avoiding a fatty meal, which inhibits absorption), they are successful in up to 80% of men with organic ED (although in only about 50–70% of men with diabetes and 50% of elderly men). Tadalafil has a longer duration of action than other PDE5 inhibitors and can also be prescribed at lower doses for continuous daily use. Unfortunately, well-performed comparisons of the available treatments for ED are not available. The literature on PDE5 inhibitors, in particular, is limited by inconsistent study designs, inclusion/exclusion criteria, dosages, treatment durations, randomization, and crossover. When assessing “success” of ED therapy, it is important to consider more than the quality of the erection or frequency of penetration, since effective but invasive interventions (i.e., intracavernosal injections) are not uniformly preferred by patients. In terms of PDE5 inhibitors, maximum doses are generally preferred to submaximum doses, and longer treatment durations are generally preferred to shorter durations. Younger men with a psychogenic origin for their ED tend to prefer tadalafil for its greater duration of action while older men with moderate or severe organic ED tend to prefer sildenafil or vardenafil for better efficacy and side effect profiles. Switching from one PDE5 inhibitor to another is sometimes beneficial for nonresponders. There may also be a place for testosterone “rescue” in patients who do not respond to PDE5 inhibitors and who also have low testosterone levels.

25. Discuss the side effects of PD5 inhibitors.

The few immediate side effects associated with PDE5 inhibitors (headache, flushing, dyspepsia, hearing loss, nasal congestion, and a blue haze in vision) rarely cause discontinuation of their use. Vardenafil, tadalafil, and avanafil cause less crossover inhibition of retinal PDE6 and are therefore associated with fewer visual side effects. Since PDE5 inhibitors cause vasodilatation similar to that of nitrates, they are contraindicated in men taking any form of nitrates. The long half-life of tadalafil (the so-called “weekend pill”) may prove to be particularly troublesome if a patient develops angina within 72–96 hours of taking it. Priapism may occur as a result of using PDE5 inhibitors. Some studies have reported a small increased risk of malignant melanoma associated with PDE5 inhibitors.

26. What drug interactions are associated with PD5 inhibitors?

Because PDE5 inhibitors are metabolized via CYP3A4, any drugs that block that enzyme (e.g., erythromycin and other macrolide antibiotics; ketoconazole and other antifungal drugs; HIV

TABLE 51.2 Showing Therapeutic Options in the Treatment of ED

	ORAL PDE5 INHIBITORS	INTRA-URETHRAL ALPROSTADIL	INTRACAVERNOUS INJECTION (ALPROSTADIL, PAPAVERINE, PHENTOLAMINE)	PENILE PROSTHESIS IMPLANTATION
Pharmacology:	• Inhibit PDE5, potentiate vasodilation by nitric oxide generated cGMP • Metabolized by CYP450, require hepatic dosing	• Synthetic vasodilator identical to PGE1 • Relaxes arterial smooth muscle • Inhibits platelet aggregation	• Agent specific • Relax smooth muscle	• Available in inflatable and noninflatable versions
Contraindications:	• Nitrate use within 24 hour (48 hour for tadalafil) • Prolonged QT (vardenafil) • Caution if using alpha blockers • Caution if penile deformity • Caution if liver/kidney disease	• Sickle cell anemia • Multiple myeloma • Leukemia • Penile deformities • Penile implants	• Sickle cell anemia • Multiple myeloma • Leukemia • Penile deformity • Penile implant	• Active systemic, cutaneous, or urinary infection
Side effects:	• Flushing • Nasal congestion • Headache • Hearing loss • Dyspepsia • Visual side effects (sildenafil, avanafil, and vardenafil) • Back pain • Mild QT prolongation (vardenafil) • Hypotension • Syncope • MI, angina • Stroke	• Hypotension • Syncope • Priapism • GU pain	• Priapism • Penile fibrosis • Hypotension • Hematoma • Ecchymosis • Penile pain • Bleeding • Angulation/ Peyronie disease	• Infection • Erosion • Mechanical failure (6–16% at 5 years) • Penile shortening • Reduced efficacy of medical therapy if prosthesis fails • Auto-inflation
Monitoring Parameters:	Creatinine at baseline	Initial dose under supervision (risk of syncope)	Initial dose under supervision, train for management of priapism	Physical exam

TABLE 51.3 Comparison of PDE5 Inhibitors*

	SILDENAFIL (VIAGRA)	VARDENAFIL (LEVITRA)	TADALAFIL (CIALIS)	AVANAFIL (STENDRA)
Onset:	20 min.	10 min.	20 min.	15 min (100 mg/ 200 mg doses 30 min (50 mg dose)
Tmax:	1 hour	45 min.	2 hours	30–45 min.
$T_{1/2}$:	3–5 hours	4–5 hours	17.5 hours	5 hours
Initial Dose:	50 mg (25 mg if >65 years old)	10 mg (5 mg if >65 years old)	2.5 mg or 10 mg	50 mg
Max Dose:	100 mg	20 mg	20 mg	200 mg
Notes:	Original PDE5 inhibitor. It has the most data on safety and efficacy. Avoid high-fat meals when dosing.	Avoid high-fat meals when dosing.	Comparable efficacy and safety when given 2.5–5 mg daily for men with intercourse >2 times per week. No dietary restriction needed. Also approved for daily use at 2.5–5 mg/day	Avoid high-fat meals when dosing

Tmax, time to maximum plasma concentration; $T_{1/2}$, half-life
*Comparative efficacy data is lacking between the four available agents. Failure of one agent is not a contraindication to trial of a different PDE5 inhibitor.

protease inhibitors, such as saquinavir and ritonavir; and cimetidine) increase the plasma concentrations of PDE5 inhibitors. In such cases, PDE5 inhibitors should be started at one-fourth to one-half of the usual dose. Since PDE5 inhibitors may potentiate the hypotensive effect of α-adrenergic blocking agents, they should be given in lower doses (sildenafil) or not at all (vardenafil) in men on alpha blockers for control of blood pressure or for benign prostatic hypertrophy. Grapefruit and grapefruit juice should be avoided within 24 hours of PDE5 inhibitor use.

27. Summarize the role of intracavernosal injections.

Intracavernosal injection of vasoactive substances (PGE, papaverine, and phentolamine) individually or in combination (Trimix) may be effective for men in whom PDE5 inhibitors have failed or are contraindicated.

28. List the surgical procedures used to treat impotence.

- Revascularization procedures
- Obliteration of venous shunts
- Penile venous stripping surgery
- Venous ligation surgery
- Surgical penile implants

29. When are intracavernosal or intraurethral injections recommended?

Injection of vasodilatory substances directly into the corpora cavernosa of the penis should be reserved for men in whom PDE5 inhibitors are ineffective, contraindicated, or limited by intolerable adverse effects. Such “PDE5 salvage” therapy results in an erection satisfactory for intercourse in some men with ED. PGE1 (Caverject), papaverine, and phentolamine may be used alone or in combination (Trimix).

30. Discuss the side effects of intracavernosal and intraurethral injections.

Side effects, which depend on the type and quantity of substances injected, include hypotension, elevation of liver enzymes, headache, penile pain, and bleeding. Local complications include hematoma, swelling, inadvertent injection into the urethra, and local fibrosis with long-term use. The most serious local complication is priapism (a sustained erection) for more than 4 hours, which may necessitate injection of alpha-adrenergic agonists or corpora cavernosal aspiration. PGE1 is also available as an intraurethral suppository (medicated urethral system for erection [MUSE]) and, since it is less invasive and easier to use, may be a more appropriate second-line agent than intracavernosal injection. No controlled studies have evaluated the success of either approach in PDE5 inhibitor failures.

31. Does the onset of ED have other health implications?

The development of ED is associated with a 45% increased risk of cardiovascular events. This is in the same range as other well-known risk factors such as current smoking and a family history of a myocardial infarction (MI). Though MI and sudden cardiac death have been reported after sildenafil use, the relationship of these outcomes with the use of this drug is not clear. The possible association of adverse cardiovascular events and PDE5 inhibitor use is confounded by sexual activity itself being a trigger for MI and earlier data from patients who used concomitant nitrates as well. Subsequent postmarketing surveillance data have not demonstrated a significant relationship between PDE5 inhibitor use and adverse cardiovascular events. Overall, the absolute risk of MI while on ED treatment is very low (20 cases per million per hour of use in prior MI patients). Therefore, known cardiac disease is not a strict contraindication to treatment, especially in low-risk patients who are able to engage in physical activity with similar levels of exertion to intercourse (3-4 METS). High-risk patients, however, should be further evaluated and stabilized prior to engaging in intercourse or undergoing treatment of ED, including:

- Unstable or refractory angina
- Uncontrolled hypertension
- Congestive heart failure
- MI or stroke in the last 2 weeks
- High-risk arrhythmias
- Hypertrophic or other cardiomyopathy
- Moderate to severe valvular disease

32. What other modalities are available to treat men with ED?

Vacuum erection devices provide a noninvasive, mechanical solution for ED. They are somewhat cumbersome to use and require the placement of an occlusive ring at the base of the penis to prevent venous outflow. They may be particularly effective in those men who have a “venous leak” as the etiology of their ED. The constrictive ring prevents antegrade ejaculation because of the urethral constriction. Surgical revascularization has a limited place in the treatment of men with ED because of its invasiveness and limited success rate. Similarly, penile prosthesis insertion is rarely done because of the availability of several effective and noninvasive alternatives. In men in whom premature ejaculation is the major problem, intermittent use of topical anesthetic agents, tramadol, and/or selective serotonin reuptake inhibitors (SSRIs) has been efficacious in delaying time to ejaculation.

33. What future treatments may be forthcoming?

A novel therapy using intracavernous injection of adipose-derived stem cells to treat ED is currently under investigation. Platelet-rich plasma has been investigated in mitigating ED due to its ability to increase vascularization. Another approach is the use of centrally acting melanocortin receptor agonists. These can be administered by nasal spray and are in clinical trials. They appear to be effective alone or in combination with PDE5 inhibitors. Another emerging technology is low-intensity shock therapy (LIST) to stimulate angiogenesis and neovascularization in the penile tissue, enhance blood flow/endothelial function, and convert PDE5 inhibitor nonresponders to responders. A similar treatment modality, low-intensity pulsed ultrasound (LIPUS) is also under investigation. Finally, novel use of metformin as an adjunct to sildenafil may improve ED in men without diabetes but who have insulin resistance.

KEY POINTS

Erectile Dysfunction

- Erections are mediated by neural and endothelial NO release, which induces vasodilation.
- The specific cause of ED can be diagnosed in 85% of men.
- Besides diabetes mellitus, the three most common endocrine causes of ED are primary hypogonadism, secondary hypogonadism, and hyperprolactinemia.
- The antihypertensives that are least likely to cause ED are ACE inhibitors, ARBs, and calcium channel blockers.
- Consider the role of risk factors, lifestyle modification, and psychological counseling in all men with ED.
- Serum prolactin levels should be measured in men with secondary hypogonadism or examination suggesting a pituitary lesion.
- Consider the possibility of concomitant cardiovascular disease in men with ED and treat unstable cardiac conditions prior to initiation of ED therapy.
- PDE5 inhibitors (sildenafil, vardenafil, tadalafil, and avanafil) are the most effective drugs for treating nonhormonal ED. Fatty meals, which can inhibit absorption, should be avoided before taking sildenafil, vardenafil, and avanafil.
- PDE5 inhibitors are contraindicated in men taking any form of nitrates, since PDE5 inhibitors can cause vasodilatation similar to that caused by nitrates.

WEBSITES

1. https://academic.oup.com/jcem/article/95/6/2536/2597900
2. https://www.ncbi.nlm.nih.gov/books/NBK562253/
3. https://www.hormone.org/diseases-and-conditions/mens-health/erectile-dysfunction
4. http://auanet.org/guidelines
5. https://my.clevelandclinic.org/health/diseases/10035-erectile-dysfunction

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CHAPTER 52

Gynecomastia

Mark Bridenstine, Brenda K. Bell, and Micol S. Rothman

1. Define gynecomastia.

Gynecomastia is defined as the presence of palpable breast tissue in a male. True gynecomastia is a benign condition resulting from enlargement of glandular breast tissue and should be distinguished from excess adipose accumulation (i.e., pseudogynecomastia).

2. How does gynecomastia present clinically?

Gynecomastia can present in infancy, puberty, or adulthood. It usually presents as a palpable discrete button of tissue arising concentrically beneath the nipple and areola. Gynecomastia feels firm, mobile, and "gritty" compared with surrounding adipose tissue. Fatty tissue, unlike gynecomastia, will not cause resistance until the nipple is reached. If any doubt remains, soap and water on the breast can facilitate the examination by decreasing skin friction.

3. What is the significance of painful gynecomastia?

Gynecomastia is frequently asymptomatic and incidentally discovered. Pain or tenderness implies recent, rapid growth of breast tissue. This may indicate a pathologic cause for the gynecomastia and should prompt further evaluation.

4. Is gynecomastia always bilateral?

The involvement tends to be bilateral, but asymmetry is common. Unilateral enlargement is present in 5% to 25% of patients and may be a preliminary stage in the development of bilateral disease. In autopsy studies, unilateral enlargement is often found to be bilateral gynecomastia histologically.

5. Summarize the pathophysiology of gynecomastia.

Gynecomastia results from an imbalance between the stimulatory effect of estrogen on ductal proliferation and the inhibitory effect of androgen on breast development. The imbalance is most commonly caused by increased production of estrogens, decreased production of testosterone, or increased conversion of androgens to estrogens in peripheral tissue. Disorders of sex hormone–binding globulin (SHBG) or androgen receptor binding and function can also result in gynecomastia.

6. Where are estrogens produced in the male?

Direct testicular production of estrogens accounts for <15% of male estrogen production. The majority of estrogens come from the conversion of adrenal and testicular androgens to estrogens by aromatase enzymes in peripheral tissues, particularly adipose tissue and the liver.

7. What is the most common cause of gynecomastia?

Asymptomatic palpable breast tissue is common in normal males, particularly in the neonate (60–90%), at puberty (60–70%, ages 12 and 15 years), and with increasing age (20–65%, age >50 years). Prevalence of histopathologically confirmed gynecomastia is up to 40% in autopsy series. Because of this high prevalence, gynecomastia is considered a relatively normal finding during these periods of life. Gynecomastia is often described as *physiologic* or *idiopathic* at these ages.

8. Why does gynecomastia occur so commonly during these stages of life?

Neonatal gynecomastia is caused by placental transfer of estrogens. During early puberty, production of estrogens begins sooner compared with testosterone production, causing a temporary imbalance in the ratio of estrogens to androgens. With aging, testosterone production decreases, and conversion of peripheral androgen to estrogen often increases because of an age-related increase in adipose tissue. There may also be a higher prevalence of offending medications and medical conditions in the elderly population.

9. What are the other causes of gynecomastia?

Patients with idiopathic or pubertal gynecomastia make up the majority of cases. Drugs account for 10% to 20% of cases and hypogonadism for another 10%. Adrenal or testicular tumors account for <3% of cases; gynecomastia may even precede the identification of the testicular tumor. Other causes combined account for <10% of cases and include androgen-resistance disorders, malnutrition, cirrhosis, alcohol abuse, renal disease, congenital adrenal hyperplasia, extragonadal tumors, refeeding gynecomastia, and hyperthyroidism. Case reports of atypical infectious etiologies (e.g., tuberculosis and filariasis) and topical exposure to essential oils (e.g., lavender and tea tree) have been described.

10. What drugs cause gynecomastia?

Many drugs have been implicated, some with well-characterized steroid effects, others noted in case reports and without a clearly elucidated mechanism (Table 52.1).

11. How do testicular tumors cause gynecomastia?

Germ cell tumors can produce human chorionic gonadotropin (hCG). Like luteinizing hormone (LH), hCG increases testicular estradiol production. Leydig cell tumors, in contrast, may directly secrete estradiol.

TABLE 52.1 Causes and Mechanisms of Gynecomastia Development

PROPOSED MECHANISM	REPORTED AGENTS
Altered Estrogen/Androgen Ratio	
Estrogen excess (exogenous)	Androgens and anabolic steroids (via aromatization of androgens to estrogens), estrogen creams and systemic formulations, human chorionic gonadotropin (hCG), digitoxin (estrogen-like activity), lavender and tea tree essential oils
Androgen deficiency/inhibition of androgen synthesis	Finasteride, dutasteride, ketoconazole, metronidazole, methotrexate, various chemotherapeutic agents, gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide, goserelin)
Decreased androgen action	Spironolactone, cimetidine, ranitidine, antiandrogen prostate cancer therapies (e.g., bicalutamide, enzalutamide, flutamide), marijuana, cyproterone acetate
Increased Prolactin	
Antidopaminergic agent	Haloperidol, risperidone, metoclopramide, domperidone, phenothiazines
Mechanism Unknown	
ACE inhibitors	Captopril, enalapril
Calcium channel blockers	Nifedipine, amlodipine, diltiazem, verapamil
Alpha-receptor blockers	Doxazosin, prazosin
Centrally acting agents	Clonidine, methyldopa, reserpine, diethylpropion, amphetamines
Statins (? inhibition of adrenal/gonadal steroid synthesis)	Rosuvastatin, lovastatin, pravastatin, simvastatin
Immunomodulatory agents	Thalidomide, imatinib, dasatinib
Antidepressants	Tricyclic antidepressants, duloxetine, fluoxetine
Antiepileptics	Phenytoin, diazepam, gabapentin
Antituberculosis agents	Isoniazid, ethionamide
Supplements	Melatonin, dong quai, hCG diet
Other	Amiodarone, protease inhibitors, proton pump inhibitors, cimetidine, ranitidine, growth hormone, fenofibrate, heroin, methadone, alcohol, minocycline, penicillamine, etretinate, theophylline, auranofin, sulindac

BOX 52.1 Significant Information to Ascertain in Patients With Gynecomastia

Age
Thyroid symptoms
Duration of enlargement
Drugs, herbs, supplements
Breast symptoms (tenderness, discharge)
Alcohol and illicit drug use

Family history of gynecomastia or breast cancer
Other illnesses
Congenital abnormalities
Nutritional status and recent changes in weight
Pubertal progression
Impotence and libido

12. What extragonadal tumors cause gynecomastia?

Pancreatic, gastric, and pulmonary tumors, transitional cell bladder carcinoma, and renal cell carcinoma have been associated with hCG production. Hepatomas may have increased aromatase activity that results in excess conversion of androgens to estrogens.

13. Who should undergo evaluation for gynecomastia?

History and physical examination are indicated in all cases and will determine the cause in 30% to 40% of patients. Gynecomastia, however, is so common that many experts are cautious about attaching importance to the detection of a small amount of breast tissue in an otherwise asymptomatic male. In adolescents, there is no reason to consider endocrine testing unless the enlargement is massive, or the gynecomastia persists for >2 years. Acute development of enlargement and tenderness in males age >20 years warrants additional evaluation, as do eccentric, hard masses and lesions >4 cm in size.

14. What information is significant in the history?

See Box 52.1.

15. What should be noted on the physical examination?

Important features include characteristics of the breast tissue (size, irregular, firm, eccentric, nipple discharge), overlying skin changes (ulceration, nipple retraction), testes (size, asymmetry), abdomen (liver enlargement, ascites, spider angiomas), secondary sexual characteristics, thyroid status (goiter, tremor, reflexes), signs of excessive cortisol (buffalo hump, central obesity, hypertension, purple striae, moon facies), and body mass index (BMI)/body habitus (bodybuilder physique, obesity).

KEY POINTS

General Approach to Gynecomastia

- The most important differentiation is between gynecomastia and breast cancer. If doubt remains after physical examination, mammography should be performed.
- Most cases are bilateral, asymptomatic, and incidentally discovered. History, physical examination, and reevaluation in 3 to 6 months are appropriate for such men.
- Rapid enlargement, size >4 cm, pain, and age <10 years or between 20 and 50 years correlate with a systemic illness/pathologic cause for the gynecomastia. Such men should be evaluated thoroughly if the cause is not apparent after history and physical examination.
- Malignant tumors can cause gynecomastia, although rarely. Consider testicular, pulmonary, and abdominal (pancreatic, adrenal, gastric, renal/bladder) tumors.

16. Should laboratory tests be ordered?

European Academy of Andrology Guidelines recommend measuring liver enzymes, renal function, thyrotropin (thyroid-stimulating hormone [TSH]), and testosterone (total and free), estradiol, sex hormone–binding globulin (SHBG), human chorionic gonadotropin (hCG), alpha fetoprotein (AFP) prolactin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). If the hCG, AFP, or estradiol level is elevated, testicular ultrasonography is indicated. If this is negative, chest radiography and abdominal computed tomography (CT) should follow. For prepubertal patients, adrenal CT would precede testicular ultrasonography. DHEA-S, karyotype, or DNA for genetic analysis such as PCR for the androgen receptor might be done if clinically indicated.

17. What findings raise the suspicion of breast cancer?

Breast cancer is rare in cisgender men (0.2%). The risk is increased in Klinefelter's syndrome (3–6%) and in male relatives of young women with breast cancer. Carcinoma is usually unilateral, painless, and nontender. Bloody discharge, ulceration, firmness, fixation to the underlying tissue, eccentric location, and adenopathy are suspicious findings. If any doubt remains, mammography or ultrasound should be considered. If there are concerns for malignancy, a core needle biopsy can be performed.

18. Will gynecomastia spontaneously regress?

Gynecomastia of recent onset and <3 cm in size will regress in 85% of patients. It may take 18 to 36 months for gynecomastia to resolve during puberty, but resolution will occur in >90% of pubertal boys. Persistence is uncommon after age 17 years. Gynecomastia caused by a medication or underlying disease should also resolve after discontinuing the inciting agent or treating the underlying disease. This should be emphasized if anabolic steroid use is suspected as an etiology. Persistent tissue becomes more fibrous with time, however, and is less likely to remit spontaneously if it has been present for >12 months. More highly developed breast tissue (Tanner stages III, IV, and V) is also less likely to regress.

19. What is the treatment when gynecomastia does not regress?

Hormonal therapy can be attempted. Testosterone should only be given to patients with true hypogonadism. Tamoxifen, raloxifene, clomiphene, and anastrozole have all been used. Although studies are small, and this is an off-label use, tamoxifen has the fewest side effects and the highest response rate for both improvement in tenderness and decrease in mass size. Partial regression can be seen in approximately 80% of patients, and one study reported resolution in 73/81 men treated with 10 mg daily of tamoxifen. Response should be assessed after 3 months of treatment. Diarrhea, constipation, and hot flashes are commonly reported adverse events, and thrombotic events, while rare, have been reported. Aromatase inhibitors, which decrease estradiol levels via blocking aromatization of testosterone, appear less efficacious and can adversely affect bone mass, body fat accumulation, and sexual function in men. Medication is more likely to work if gynecomastia has been present for <4 months and the size of the tissue is <3 cm. For recurrent or persistent gynecomastia >3 cm, surgery is the recommended therapy. Suction lipectomy can be done for more mild cases whereas a more extensive resection may be required for more severe cases.

20. Are there populations where other treatment options might be considered?

Men with prostate cancer frequently experience gynecomastia during antiandrogen treatment. SERMS, AI, and low-dose bilateral breast irradiation have been examined. Prophylactic radiation therapy and daily tamoxifen appear to the most effective treatments in this population.

KEY POINTS

Treatment of Gynecomastia

- Most cases resolve spontaneously or after removal of the offending medication or treatment of the underlying disease.
- Medical management with tamoxifen can be attempted for 3 to 6 months, if desired.
- The longer the tissue has been present and the larger the amount of tissue, the less likely is the response to tamoxifen. Surgery is indicated in these cases.

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Amenorrhea

Micol S. Rothman and Margaret E. Wierman

1. Define amenorrhea.

Amenorrhea is the absence of menstrual periods. *Primary amenorrhea* is the failure to ever begin menses; *secondary amenorrhea* refers to the cessation of menstrual periods after cyclic menses have been established. *Oligomenorrhea* refers to lighter and less frequent menses.

2. Describe the normal timing of puberty.

Puberty in girls is usually heralded by the initiation of breast development (thelarche). The age of thelarche has been noted to be downtrending, but typically menarche occurs 2–3 years after thelarche. Ninety-five percent of girls experience onset of puberty between 8.5 and 13 years of age in most populations, and much of this is determined by genetics. The average age for girls in the United States to begin menses is 12 years. Although previous data suggested differences in the onset of sexual maturation among racial and ethnic groups, more recent data suggest BMI may be the important driver, rather than race or ethnicity.

3. Summarize the underlying process of pubertal development.

Pubertal development is triggered by Kisspeptin activation of gonadotropin-releasing hormone (GnRH)–induced episodic secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) from the pituitary gland. The pulsatile release of gonadotropins activates the ovaries, causing the maturation of follicles and the production of estrogen and, later, progesterone. These gonadal steroids feed at the level of the hypothalamus and pituitary to regulate GnRH and gonadotropin secretion. A final maturation event is the development of positive feedback by estradiol levels to induce the midcycle LH surge that stimulates ovulation. In many adolescents, menstrual cycles are anovulatory, and thus irregular, for the first 12–18 months. As the hypothalamic–pituitary–gonadal (HPG) axis matures, ovulatory cycles become more frequent. Typically, all but one or two cycles per year are ovulatory in premenopausal women.

4. What types of disorders cause primary amenorrhea?

Primary amenorrhea is defined as a lack of menses by age 16 years or a lack of secondary sexual characteristics by age 14 years. It usually results from abnormal anatomical development of the female reproductive organs or from a hormonal disorder involving the hypothalamus, pituitary gland, or ovaries (Table 53.1).

5. What are the hypothalamic and pituitary causes of primary amenorrhea?

Congenital hypogonadotropic hypogonadism (CHH) can be caused by maturational arrest of GnRH-producing neurons during embryonic development (also called Kallmann syndrome when associated with anosmia) or failure of GnRH secretion at the time of puberty. The Kisspeptin/Kiss receptor system has recently been shown to regulate GnRH secretion at puberty. Mutations in this pathway, as well as the GnRH receptor in the pituitary, may also cause failure of or impaired sexual maturation. Pituitary tumors, craniopharyngiomas, and Rathke's pouch cysts can cause impaired LH and FSH secretion in adolescence, disrupting sexual maturation.

6. Summarize the ovarian causes of primary amenorrhea.

The ovarian function may be impaired because of gonadal dysgenesis caused by Turner syndrome (45X karyotype) or destruction by chemotherapy or radiation before the completion of sexual maturation. The presence of ambiguous genitalia or palpable gonads in the labia or inguinal area may indicate a difference in sexual differentiation, such as congenital adrenal hyperplasia (CAH) (21-hydroxylase deficiency) or an androgen resistance syndrome (previously known as testicular feminization) resulting from mutations in the androgen receptor.

TABLE 53.1 Causes of Primary Amenorrhea

- Anatomic
  - Congenital absence of ovaries, uterus, or vagina
  - Cervical stenosis
  - Imperforate hymen
- Hormonal
  - Hypothalamic
  - GnRH deficiency
  - Hypothalamic tumor (craniopharyngioma)
- Pituitary
  - Prolactinoma
  - Rathke's cleft cyst
  - Panhypopituitarism from a genetic mutation
- Ovarian
  - Gonadal dysgenesis (XO)
  - Chemotherapy or radiation damage of the ovaries
  - Androgen resistance/insensitivity syndromes (XY)
- Other: congenital adrenal hyperplasia

TABLE 53.2 Causes of Secondary Amenorrhea

- Pregnancy
- Hypogonadotropic hypogonadism
- Hyperprolactinemia (resulting from drugs or prolactinoma)
- Pituitary tumor inhibiting gonadotropin production
- Hypothalamic amenorrhea
- Hypergonadotropic hypogonadism
- Premature ovarian insufficiency (surgical or autoimmune)
- Gonadotropin-producing pituitary tumors
- Hyperandrogenic anovulation

7. What disorders cause secondary amenorrhea?

Secondary amenorrhea, which is much more common than primary amenorrhea, occurs in the post-pubertal period. The causes are outlined in Table 53.2. Pregnancy should be excluded in all women with amenorrhea. The onset of irregular menses after prior regular menses with associated hot flashes should suggest premature ovarian insufficiency (POI; i.e., premature menopause). Hypothalamic amenorrhea occurs in 3–5% of women and is caused by abnormal GnRH-induced gonadotropin secretion, often as a result of stress or energy imbalance, but is a diagnosis of exclusion. Hyperprolactinemia caused by medications or pituitary tumors occurs in 10% of women with amenorrhea. Other pituitary tumor subtypes can also result in secondary amenorrhea. Hyperandrogenic anovulatory disorders such as polycystic ovary syndrome (PCOS), CAH, and, rarely, gonadal or adrenal tumors are usually associated with oligomenorrhea, rather than amenorrhea, associated with signs and symptoms of excess androgens, such as hirsutism and acne.

8. How do you evaluate a patient with amenorrhea?

One must determine whether the disorder is anatomic or hormonal, congenital or acquired, and where the defect is located. A complete history and physical examination provide the first essential clues. Pregnancy testing should always be ordered. Timed measurement of serum gonadotropin levels (LH and FSH) should be performed within the first 5 days after the onset of spontaneous or induced menses. However, it should be noted that patients who have been on hormonal contraceptives may need to wait at least a cycle to ensure accurate results. Patients with low or normal levels of LH and FSH (hypogonadotropic hypogonadism) have a disorder at the level of the hypothalamus or pituitary gland. In contrast, patients with high LH and/or FSH levels (hypergonadotropic hypogonadism) may have a defect at the level of either the ovary (high FSH/LH) or hypothalamic-pituitary unit (high LH/FSH; e.g., PCOS), in which the hypothalamic GnRH pulse generator is abnormally accelerated or there is a gonadotrope pituitary tumor that secretes the gonadotropins, FSH, and/or LH.

Other laboratory tests to consider include measurement of a prolactin level to exclude hyperprolactinemia and thyroid function tests to exclude thyroid disorders. In a patient with signs of excess androgens, dehydroepiandrosterone sulfate (DHEA-S) and testosterone levels should be obtained. In the appropriate patient, hypercortisolism causing Cushing syndrome should be excluded with a 1-mg dexamethasone suppression test or late-night salivary cortisol testing. Exclusion of this disorder may require more than one test.

9. Discuss the major congenital causes of hypogonadotropic hypogonadism.

Congenital hypogonadotropic hypogonadism (CHH) is caused by GnRH deficiency. Female patients present with primary amenorrhea and lack of secondary sex characteristics. When associated with anosmia, the disorder is termed *Kallmann syndrome.* GnRH deficiency estimates have differed by population examined but occur more frequently in males than females and may be X-linked, autosomal dominant, autosomal recessive, or sporadic. The X-linked form is associated with a mutation in the *KAL-1* gene, which encodes anosmin, a neural cell adhesion protein thought to be important in providing the scaffolding for GnRH neurons in their migration from the olfactory placode to the hypothalamus during embryonic development. Similarly, mutations in FGF8 or its receptor FGFR1 also disrupt neuronal and olfactory nerve migration. Thus, GnRH neurons fail to reach their target in the hypothalamus. All other hypothalamic–pituitary function is normal. Recently, investigators have found that mutations in the Kisspeptin/KissR system that mediates GnRH secretion at puberty and mutations in the GnRH receptor at the level of the pituitary can also cause CHH. There are over 40 gene mutations associated with disorders of sexual development, but the majority of causes are still unknown. In these young women, estrogen administration is used to initiate the development of secondary sexual characteristics, and fertility can be attained using pulsatile GnRH or gonadotropin therapy. Despite a congenital etiology, recent data suggest that the hypogonadism in a subset of patients with CHH may be reversible, more commonly in males than females. There are no clear predicting factors.

10. What are the most frequent acquired forms of amenorrhea caused by hypogonadotropic hypogonadism?

- Hyperprolactinemia
- Hypothalamic amenorrhea

11. How does hyperprolactinemia cause amenorrhea?

Elevated prolactin levels may be caused by prolactinomas, hypothyroidism, medications (usually psychotropic drugs), or pregnancy. Hyperprolactinemia impairs the normal function of the HPG axis at multiple levels, but the major site of inhibition is the hypothalamic GnRH pulse generator. As prolactin levels rise, luteal phase defects develop, ovulation ceases, and menstrual cycles become shorter and irregular. Higher levels of prolactin are associated with amenorrhea. Treatment of the underlying cause of the elevated prolactin level usually normalizes the menstrual cycle.

12. What is hypothalamic amenorrhea?

Hypothalamic amenorrhea refers to amenorrhea resulting from acquired disorders of the GnRH pulse generator. Excessive stress and energy imbalance have been shown to act centrally to disrupt the GnRH-induced pulsatile gonadotropin secretory pattern. In men, GnRH-induced LH pulses normally occur every 2 hours. In contrast, the LH pulse pattern in women must change across the menstrual cycle, accelerating from every 90–60 minutes across the follicular phase to every 30 minutes at ovulation and then slowing from every hour to every 4–8 hours across the luteal phase. Disruption of this precisely timed pattern results in anovulation, irregular menses, and, eventually, amenorrhea.

13. What types of GnRH pulse generator defects cause hypothalamic amenorrhea?

Hypothalamic amenorrhea may result from several types of gonadotropin secretory disorders. Some women with anorexia nervosa have absent GnRH-induced LH pulsations (prepubertal pattern), some have pulsations only at night (early pubertal pattern), and still others have LH pulses throughout the 24-hour period, but they are significantly reduced in amplitude or frequency.

14. How do you make a diagnosis of hypothalamic amenorrhea?

The diagnosis depends on excluding other causes of amenorrhea and then relies heavily on a history of weight loss, high levels of exercise, or stress, with a suspicion of energy imbalance. Supportive findings on physical examination include evidence of decreased estrogen effects on the vaginal mucosa and the absence of other major illnesses. Laboratory testing usually reveals low serum estradiol and low or low-normal serum LH and FSH levels; the test for beta-hCG is negative, and the prolactin level is normal. Elevated FSH levels with low estradiol levels, in contrast, indicate probable POI.

15. What are the consequences of estrogen deficiency?

Short-term consequences of estrogen deficiency may include painful intercourse, hot flashes, and sleep disturbances. Among the more important long-term consequences may be endothelial dysfunction with early coronary disease, low bone mass, and neurocognitive dysfunction.

16. What treatment options are available for hypothalamic amenorrhea?

Interventions to reduce stress and to balance nutritional intake with a degree of exercise should be attempted initially. If these interventions are unsuccessful, estrogen therapy can be instituted. However, data are mixed as to the protective effect of estrogen on bone health in women with anorexia nervosa. Endocrine Society guidelines suggest avoiding ethinyl estradiol and treating it with transdermal estrogen and cyclic progesterone in the subset of patients with anorexia. It should be noted that this regimen does not provide contraception and may be associated with irregular bleeding in women with more mild defects. Fertility, if desired, may be achieved by ovulation induction with clomiphene in mild cases or with human menopausal gonadotropins or pulsatile GnRH administration if the disorder is more severe.

17. What disorders cause amenorrhea with hypergonadotropic hypogonadism?

- Premature ovarian insufficiency (high FSH, later high LH, and low estrogen)
- PCOS (low FSH, high LH, and normal estrogen)
- Gonadotropin-secreting pituitary tumors (high FSH and/or LH, often in postmenopausal women with low estrogen)

18. How do you make a diagnosis of POI?

POI, which is defined as menopause before age 40 years, may be caused by surgical removal or autoimmune destruction of the ovaries. Autoimmune destruction of the ovaries is characterized by a history of normal puberty and regular menses followed by the early onset of hot flashes, irregular menses, and eventual amenorrhea. Elevated serum FSH levels are the laboratory hallmark of gonadal failure resulting from loss of inhibin. To avoid misdiagnosis, blood for FSH and estradiol should be drawn in the early follicular phase (day 1–5 after onset of spontaneous or induced menses), because FSH levels rise along with LH at midcycle in normally ovulating women. Patients with Turner syndrome and mosaic karyotype (X/XX) may have several menses before they undergo menopause; therefore, a karyotype may be helpful if ovarian failure occurs in adolescence or the early 20s. Measurement of antiMüllerian hormone (AMH) may predict the age of menopause and assess for premature ovarian insufficiency. AMH is produced by granulosa cells in the ovary and decreases over time with eventual absence at the time of menopause. However, it is important to realize that AMH is a marker of ovarian follicle number, and thus, in hypothalamic amenorrhea, AMH is also low (low FSH, low E2), whereas with premature ovarian insufficiency, or at menopause the patients have low AMH, with high FSH and low E2.

19. What other disorders may coexist with POI?

Both patients and family members are at risk for other autoimmune disorders, including primary adrenal insufficiency (Addison's disease), autoimmune thyroid disorders (Graves' disease, Hashimoto's thyroiditis), type 1 diabetes mellitus, pernicious anemia (vitamin B_{12} deficiency), celiac sprue (often with vitamin D and iron deficiencies), and/or rheumatologic disorders. Testing for fragile X may be considered in certain patients.

20. What are the treatment options for women with POI?

Estrogen therapy, in combination with progesterone, is used to decrease postmenopausal bone loss and premature coronary artery disease. Options for fertility in women with POI include incubation of donor eggs with sperm with *in vitro* fertilization protocols, along with hormonal preparation of the patient to enable her to carry the fetus.

21. What is hyperandrogenic anovulation?

Hyperandrogenic anovulation refers to the cluster of disorders that present with irregular menses or amenorrhea and signs of androgen excess, such as hirsutism and acne. The disorders in this group include PCOS, androgen-secreting tumors of the ovaries or adrenal glands, Cushing's syndrome, congenital adrenal hyperplasia CAH (classic or nonclassical), and obesity-induced. PCOS is the most common disorder of this type, described in 6% to 10% of reproductive-age women. This is described in more detail in Chapter 38.

22. How do tumors cause hyperandrogenic anovulation?

Androgen-producing ovarian and adrenal tumors are suggested by the history of a rapid progression of hirsutism and virilization (temporal hair recession, clitoris enlargement, and breast atrophy), as well as high serum androgen levels (testosterone or DHEAS). They are usually associated with serum testosterone levels >200 ng/dL or DHEAS levels >900 ng/mL. However, there is no level of testosterone or DHEAS that absolutely confirms or excludes the diagnosis. The diagnosis of these tumors depends on accurate imaging studies (usually transvaginal ultrasound or adrenal CT scan).

23. What clinical and biochemical features suggest a patient with hirsutism has CAH?

CAH (most commonly caused by 21-hydroxylase deficiency) presents in infancy with ambiguous genitalia in girls and occasionally with salt-wasting syndromes. Milder forms present in adolescence with early pubarche and irregular menses. CAH is diagnosed by high basal (>2–3 ng/mL) or adrenocorticotropic hormone (ACTH)–stimulated (>10 ng/mL) levels of 17-hydroxyprogesterone, with the test performed in the follicular phase. This is an important etiology of amenorrhea that should be excluded before a diagnosis such as PCOS is given to a patient. See Chapter 38.

24. When should you suspect obesity-induced hyperandrogenic anovulation?

Obesity-induced hyperandrogenic anovulation is suggested by a history of normal puberty and menses until progressive weight gain triggers the development of hirsutism, acne, oligomenorrhea, and, later, amenorrhea. Affected women have low serum levels of FSH and LH in the follicular phase in contrast to women with PCOS (see subsequent discussion).

25. Describe the pathophysiology of obesity-induced hyperandrogenic anovulation.

Fat tissue contains aromatase and 5-alpha-reductase enzymes. Aromatase converts androgens to estrogens; when aromatase is present in increased amounts, as in obesity, constant (rather than fluctuating) serum estrogen levels are produced, inhibiting LH and FSH secretion and thereby impairing normal ovulation. Increased activity of 5-alpha-reductase, which converts testosterone to dihydrotestosterone (DHT), results in excessive DHT production, promoting the development of hirsutism and acne. Primary treatment with weight loss often results in the restoration of normal reproductive function.

KEY POINTS

Amenorrhea

- Amenorrhea with long-term estrogen deficiency can result in low bone mass and premature cardiovascular disease.
- Hyperprolactinemia and hypothalamic amenorrhea are the most common causes of acquired amenorrhea with low estrogen and low FSH levels.
- POI is an autoimmune disease; affected females are at risk for other autoimmune disorders, such as adrenal and thyroid disease, pernicious anemia, celiac sprue, and rheumatologic disorders.
- *Hyperandrogenic anovulation* refers to amenorrhea with hirsutism and acne.
- PCOS is the most common type of hyperandrogenic amenorrhea, associated with risks of infertility, endometrial cancer, metabolic syndrome, and type 2 diabetes.

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CHAPTER 54

Polycystic Ovary Syndrome

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1. How does the patient with PCOS present clinically?

Polycystic ovary syndrome (PCOS) is a multisystem condition, and individuals can present with a variety of symptoms including amenorrhea, oligomenorrhea, infertility, acne, hirsutism, alopecia, difficulty with weight loss, and, rarely, endometrial hyperplasia or carcinoma. Symptoms typically present in adolescence with irregular menses and dermatologic concerns, although many women do not seek care until adulthood when they experience infertility. In addition to common dermatologic complaints of acne and hirsutism, other findings including acanthosis nigricans, excess skin tags, hidradenitis, pilonidal cysts, and androgenic alopecia can be present. Finally, PCOS is highly associated with excess weight, and women may seek care when experiencing difficulty with weight loss.

2. Describe the pathogenesis of PCOS.

The primary intrinsic disorder causing PCOS is still debated among experts. There are three prevailing theories for the cause of hyperandrogenism: (1) primary ovarian dysfunction, (2) insulin resistance and hyperinsulinism inducing thecal cell hypertrophy, and (3) hypothalamic/pituitary dysfunction causing increased luteinizing hormone (LH) production. All these pathways appear to contribute to the pathophysiology and clinical manifestations of PCOS.

An insulin-mediated mechanism contributing to hyperandrogenism, anovulation, and other metabolic manifestations of the syndrome has been described. At least 40–70% of women with PCOS, regardless of body mass index, are insulin resistant and display compensatory hyperinsulinemia. Ovarian androgen production seems to be partly dependent on insulin and may be hyperresponsive to insulin, even in lean and normoinsulinemic women.

Ovarian and adrenal hyperresponsiveness to LH and adrenal corticotropic hormone (ACTH) are important characteristics in PCOS. Women with PCOS often have an increased LH/follicle-stimulating hormone (FSH) secretory ratio, resulting in multiple ovarian follicle recruitment, without dominant follicle development and inability to trigger a gonadotropin-releasing hormone (GnRH)-induced LH surge. This results in anovulation and the appearance of multiple subcapsular cysts. The abnormal GnRH pattern triggers constant estrogen and enhanced androgen production by the ovaries. Additionally, excess anti-Mullerian hormone (AMH), which is released by excess follicles, may inhibit GnRH secretion.

Genome-wide studies have demonstrated an underlying polygenetic predisposition to the ovarian dysfunction and insulin resistance. Women with PCOS often have a family history of PCOS or type 2 diabetes. Additionally, PCOS development may be related to intrauterine exposures such as maternal obesity, poor fetal growth, and the prenatal environment including maternal androgen and AMH concentrations.

3. What are the criteria for diagnosis of PCOS in adults?

PCOS should be diagnosed per the 2023 international consensus guidelines that incorporate previous NIH and Rotterdam criteria, as shown in Table 54.1. These 2023 consensus guidelines added elevated AMH as diagnostic criteria that could be used in place of ultrasound criteria.

4. What are the criteria for diagnosis of PCOS in adolescents?

Adolescents must meet these three criteria in order to be given a diagnosis of PCOS:

- Menstrual abnormalities defined as (a) oligomenorrhea with <9 menses a year or >90 days between menses at least 1-year post menarche or (b) primary amenorrhea after the age of 15 years or 3 years post thelarche.
- Clinical (acne/hirsutism/androgenic alopecia) and/or biochemical evidence of hyperandrogenism.

TABLE 54.1 The Most Common Guideline Based Diagnostic Criteria for PCOS are Shown

MEASUREMENT	NIH 1990	ROTTERDAM 2003	INTERNATIONAL CONSENSUS GUIDELINE 2023
Oligomenorrhea (eight or fewer menses a year)	+	±	±
Hyperandrogenism (clinical or biochemical, testosterone)	+	±	±
Polycystic ovary on ultrasound (greater than 10 mL size and >12 follicles)	±	±	±
Elevated AMH (above upper limit per assay)	NA	NA	±
To meet the criteria for PCOS	Must have the first two	Needs two of three	Both top two or one of top two and US or AMH

NIH, National Institute of Health; *AMH,* anti-Mullerian hormone; *US,* ultrasound.

- No other cause for irregular menses or signs of hyperandrogenism.

Distinct from adults, there is no role for ovarian ultrasound or AMH in adolescents to confirm the diagnosis of PCOS, as normative data for follicle count, ovarian size, and AMH are not well established for this age group. Ultrasound can be useful to investigate anatomic causes of primary amenorrhea, and thickness of the endometrial lining in case of failure to have a withdrawal bleed after a progesterone challenge, or in cases of ovarian pain with a suspected cyst or torsion but should not be ordered for diagnosis of PCOS. The original Rotterdam ovarian criteria were developed from women with a mean age of 28 years. Follicle count peaks in early adolescence, thus normative adult values cannot be applied to adolescents. Further, abdominal ultrasounds are not as accurate as vaginal ultrasounds, especially in individuals with obesity.

5. What are the long-term consequences of PCOS?

Long-term consequences of PCOS include reproductive, cardiometabolic, and psychosocial conditions. Reproductive consequences include not only infertility but also higher rates of pregnancy complications and endometrial cancer, especially in those with prolonged oligomenorrhea.

Cardiometabolic disease is higher in women with PCOS, especially when obesity is present. The relative risk of developing type 2 diabetes is two- to eightfold higher and metabolic dysfunction–associated steatotic liver disease (MASLD) is two- to fourfold higher, regardless of BMI but with greater risk in those with obesity. Risk factors for cardiovascular disease, including hypertension, hyperlipidemia, early atherosclerosis deposition, and endothelial dysfunction, are present in younger women with PCOS. Once postmenopausal, there are increased rates of myocardial infarction, stroke, and cardiovascular disease–related death. Obstructive sleep apnea is more common.

Women with PCOS have a high prevalence of depression, anxiety, and disordered eating. Sexual dysfunction can arise from poor body image, underlying mood disorders, infertility, and therapies used to treat PCOS.

6. How is hyperandrogenism defined and what can affect measurements of testosterone?

Hyperandrogenism is defined as having serum testosterone values in excess of the laboratory-defined normative data, as a standardized range does still not exist. Many women will also have a mildly elevated dehydroepiandrosterone sulfate (DHEA-S). Testosterone has a strong diurnal rhythm, and laboratory studies should be done in the morning to catch the peak value, ideally before 10 a.m. Testosterone rises during ovulation and thus is best checked in the first 5 days of the cycle in women who are having cycles. Sex hormone–binding globulin (SHBG) can be decreased with obesity, and thus a free testosterone or a calculated free androgen index is ideal in women with obesity. Testosterone assays are problematic, and total testosterone should be measured with liquid chromatography / tandem mass spectroscopy and free testosterone with equilibrium dialysis.

TABLE 54.2 Other Conditions Which Can Cause Menstrual Cycle Irregularities or Symptoms of Hyperandrogenism Which Must be Ruled Out in Order to Make a Diagnosis of PCOS

CONDITION	LABORATORY TESTING	OTHER SIGNS
Pregnancy	↑HCG	
Prolactinoma	↑Prolactin	Galactorrhea; breast enlargement/ tenderness; visual field defects
Hypothyroidism	↑Thyroid-stimulating hormone and normal or ↓thyroxine	Constipation; dry skin; fatigue
Primary ovarian failure	↑Luteinizing hormone, ↑follicle-stimulating hormone, ↓Estradiol	Hot flashes; vaginal dryness
Hypothalamic amenorrhea	↓Luteinizing hormone, ↓follicle-stimulating hormone, ↓Estradiol	Excess exercise; BMI extremes (high or low)
Congenital adrenal hypoplasia	↑Morning 17-hydroxyprogesterone	Premature adrenarche; short stature for family; family history
Androgen-secreting tumors	↑DHEAS, ↑androstenedione	
Cushing's syndrome	↑Overnight salivary cortisol, ↑24-hour urine cortisol, ↑AM cortisol after 1-mg dexamethasone suppression test	Central obesity; rapid-onset symptoms; thick, violaceous striae; proximal muscle weakness
Exogenous Androgens	History, ↑testosterone	

↑, Increased; ↓, decreased; *HCG,* human chorionic gonadotropin; *BMI,* body mass index; *DHEAS,* Dehydroepiandrosterone sulfate.

7. What is the differential diagnosis for suspected PCOS?

PCOS is a diagnosis of exclusion. Other etiologies for hirsutism and amenorrhea need to be excluded and are shown in Table 54.2.

8. What is the role of obesity in PCOS?

PCOS can develop across the weight spectrum; however, there is an increase in the prevalence of PCOS in individuals with BMI >30 kg/m^2. Rates of PCOS have been increasing in parallel with the obesity epidemic. Additionally, symptoms of hyperinsulinism and hyperandrogenism are exacerbated with increased weight leading to more significant clinical findings in patients with obesity, making them more likely to seek medical advice.

9. What metabolic screening needs to be done in PCOS?

Women with PCOS are at increased risk for metabolic disease including insulin resistance, type 2 diabetes, MASLD, hyperlipidemia, and cardiovascular disease. Women with PCOS should have a 2-hour 75-g oral glucose tolerance test at diagnosis, then every 1–3 years and prior to pregnancy, regardless of weight. A hemoglobin A1c is a less accurate but also acceptable test for hyperglycemia. MASLD should be screened with an ALT and follow-up imaging per current hepatology guidelines–recommended screening based on age. A fasting lipid panel should be checked annually, blood pressure obtained at every visit, and a history of modifiable cardiovascular disease risk factors elicited.

10. What other conditions need to be screened for in women with PCOS?

Psychiatric Disease: Women with PCOS have higher rates of psychiatric disease including both depression and anxiety. These tend to be worse in women with more extreme dermatologic manifestations or undergoing infertility treatments. Assessment for disordered eating behaviors and sexual dysfunction should be performed.

Disordered Sleep: Women with PCOS have a more than twofold increased risk for obstructive sleep apnea compared to weight-matched controls. Untreated sleep apnea can contribute to metabolic disorders, mood alterations, increased appetite, fatigue, and difficulty losing weight. All women should be screened with questions regarding the quality of sleep and polysomnograms ordered in those who have symptoms suggestive of obstructive sleep apnea. Obstructive sleep apnea should be treated in those with a confirmed diagnosis.

Endometrial Cancer: Women presenting later in life with a longer history of irregular menses are at increased risk for endometrial cancer. Screening is discussed below.

11. Which patients need counseling on lifestyle modification?

Healthy lifestyle recommendations should be given to all women with PCOS regardless of weight. Whereas diet and exercise may have less of an effect in normal-weight women with PCOS in terms of normalization of menses, a healthy lifestyle will still modulate the risk for associated cardiometabolic disease. In women with obesity, up to 60% can have normalization of menses and decreases in testosterone if they achieve an 8–10% loss in body weight. However, metabolic improvements can be seen even in the absence of weight loss.

12. What is the most effective lifestyle modification for women with PCOS?

Per obesity literature, the most effective lifestyle intervention is one that the patient can maintain, and every effort should be made to develop a personalized and multidisciplinary approach to ensure optimal patient success. Overall dietary recommendations include caloric restriction; to date, there are no specific macronutrient recommendations for PCOS per se, although diets low in concentrated sugar and fructose are beneficial for those with glucose intolerance, hypertriglyceridemia, and MASLD. There should be an emphasis on higher-quality carbohydrates with lower glycemic indices and higher fiber content. There is no conclusive evidence for using any nutritional supplementation for PCOS, although standard guidelines for vitamin D should be followed.

The first approach to exercise should be an increase in baseline activity, as women who do not exercise regularly may have significant deconditioning. This should be gradually increased to 150–300 minutes of moderate-intensity or 75–150 minutes of vigorous-intensity aerobic activity weekly with 2 days of muscle strengthening per week. Physical activity can include walking, physical chores, playing games, and more intense aerobic activities such as running or dance exercise classes, high-intensity interval training, and sports. Personalizing an exercise program to fit an individual's life is paramount for success.

13. What are the pregnancy complications found in women with PCOS?

Pregnant women with PCOS are at increased risk for numerous adverse pregnancy outcomes including increased rates of gestational diabetes, hypertension, preeclampsia, intrauterine growth restriction, small for gestational age (SGA), miscarriage, preterm delivery, and c-section. Many of these risks are even higher in those with prepregnancy obesity. The use of assisted reproductive technology does not increase the underlying risk further. Preconception care should include screening for hyperlipidemia and hypertension. Underlying diabetes status should be assessed preconception or at the first prenatal visit and again screened at 24–28 weeks to capture new-onset gestational diabetes. Increased monitoring for hypertension and preeclampsia should occur after 30 weeks of gestation.

14. Does PCOS affect menopause?

The diagnosis of PCOS in perimenopause and menopause is challenging and needs to be made based on the past history of irregular menses and hyperandrogenism symptoms. New presentations of hyperandrogenism should be evaluated for androgen-secreting tumors and ovarian hyperthecosis. It has been shown that women with PCOS may have a slightly later menopause. Usually, symptoms of PCOS tend to attenuate around menopause, with a natural age–related decline in androgen production and ovarian follicle attrition. However, because the risk of cardiometabolic complications will still be present, it is important to consider the diagnosis, prevention, and treatment of these complications.

15. What are the treatment options for patients with PCOS not desiring pregnancy?

The initial therapy goals should be personalized to address what the patient identifies as their primary complaint. Combined contraceptive methods such as oral contraceptive pills (OCP), patches, and vaginal rings can be used for the management of irregular menses and dermatologic manifestations such as hirsutism, acne, or alopecia. For menstrual regulation and prevention of endometrial hyperplasia alone, cyclic progesterone, a levonorgestrel implant, or hormonal intrauterine devices can also be utilized. Metformin can be used either in combination with or as an alternative to OCPs; it has less efficacy for the management of hyperandrogenism but better efficacy for improving metabolic markers. Weight loss–focused medications such as phentermine/topiramate, bupropion/naltrexone, and glucagon-like-peptide-1 receptor agonists (GLP1-RA) can assist patients in reaching weight loss goals. GLP1-RA shows promise in PCOS for reducing testosterone, improving menstrual cycles, and some metabolic and androgen outcomes. Bariatric/metabolic surgery can lead to improvement in weight, metabolic complications, ovulation, and pregnancy rates. Concurrent effective contraception should be used with all weight loss medications and procedures, as they have not been shown to be safe in pregnancy.

16. What are the treatment options for dermatologic manifestations?

For dermatologic manifestations directly related to the increased androgens (acne, hirsutism, and androgenic alopecia), the best therapy is to restore a normal estrogen-to-testosterone ratio with estrogen therapy using combined oral contraceptives, estrogen patches, or vaginal rings. Androgen receptor blockers, such as spironolactone, and topical therapy with eflornithine can be beneficial, although they do not reverse previous long-term changes in hair follicles. More definitive therapies such as electrolysis and laser hair reduction can be encouraged. Minoxidil topical or oral therapy is helpful for women experiencing androgenic alopecia.

Standard over-the-counter acne therapies with salicylic acid or benzoyl peroxide are first line. Severe acne can necessitate consultation with a dermatologist for courses of antibiotics, topical retinoids, or oral isotretinoin in cases of severe cystic acne. Many of these therapies are teratogenic and cannot be used in women desiring fertility.

For women with hidradenitis or folliculitis, the wearing of properly fitting clothes and undergarments made of absorptive material such as cotton is critical. Topical cleaning with chlorhexidine can be combined with the application of topical antibiotics and/or oral antibiotics in cases of abscesses or more severe infections. Extreme cases are treated with a TNFα inhibitor.

The appearance of acanthosis nigricans and confluent and reticulated papillomatosis (CARP) can be reduced with metformin and topical treatment with 12–15% lactic acid. Oral doxycycline or minocycline for a duration of 3–6 months can also be used to reduce the discoloration of CARP.

17. What are the risks and benefits of hormonal therapies in women with PCOS?

Combined hormonal contraceptives (pill, patch, or vaginal ring) are effective for regulating menses and treating dermatologic manifestations in PCOS. Women with PCOS are thought to have a slightly higher thrombotic risk, and thus standard screening for thrombotic risk factors such as personal or family history of stroke and complex migraines with aura is critical. The role of long-term combined contraception therapy in cardiovascular disease risk in PCOS is not clear. Whereas overall population studies indicate that combined oral contraceptives do not cause weight gain, each patient will be different; some women will gain weight while other women may lose weight. Hormonal contraception may worsen insulin resistance, which should be considered in women with obesity and signs of insulin resistance or hyperglycemia. Some women experience worsening symptoms of hirsutism and acne with levonorgestrel. Finally, mood disorders can be exacerbated by any systemic hormonal contraception. Preliminary data indicates that the newer oral estrogen formulation, estetrol, may have less deleterious metabolic effects compared to ethinyl estradiol.

18. Is there a role for metabolic medications in the treatment of women with PCOS?

Reducing insulin resistance and serum insulin concentrations with metformin or other insulin sensitizers results in improvement of serum androgen levels, decreased blood pressure, improved lipids, improvement in menstrual regularity, and better glucose tolerance. However, metformin takes time to reach its full impact on hyperandrogenism symptoms and can take up to 6 months to improve menstrual cyclicity and reduce testosterone levels. Metformin is recommended to treat PCOS in women with impaired glucose tolerance or diabetes, which may represent more than 20–40% of women with PCOS.

The thiazolidinedione class of insulin sensitizers produces greater improvement of metabolic and hyperandrogenism symptoms in PCOS compared to metformin, but weight gain, cardiovascular concerns, and risk of osteoporosis have limited their use.

Phentermine/topiramate, bupropion/naltrexone, and orlistat can induce modest weight loss with some improvements in metabolic measures and fasting testosterone levels.

GLP1-RA has shown promise for decreasing androgen levels, improving metabolic measures, and restoring menstrual regularity. The majority of studies were done with older-generation GLP1-RA (exenatide and liraglutide), but limited studies with newer agents, such as semaglutide, demonstrate a greater impact on symptoms, androgens, and metabolic disease. However, weight regain after cessation of GLP1-RA remains a concern, and the effect of fetal exposure is unclear.

19. What are the treatment options for maintaining endometrial health?

Because chronic anovulation leads to an increased risk of endometrial hyperplasia and cancer, it is important to ensure cyclic endometrial proliferation and/or daily progestin exposure. There are several options available to cause cyclic shedding: combined hormonal contraceptives in pill, patch, or vaginal ring forms or intermittent progesterone. The combined contraceptives have the advantage of reducing hyperandrogenism and thereby improving acne and hirsutism. Intermittent progesterone for 10–14 days per month or two will also provide endometrial protection but has side effects that may limit utilization in these patients; furthermore, this does not provide contraception. Long-acting progestins such as the levonorgestrel intrauterine device or slow-release implant as well as low-dose daily oral norethisterone or norethindrone cause endometrial thinning and are also thought to be effective for the prevention of endometrial hyperplasia long term. Metformin may increase cyclicity and ovulation, which provides endometrial protection but may take 3–6 months to be effective.

20. What are the indications for endometrial biopsy in women with PCOS?

Women with PCOS are at threefold increased risk for the development of endometrial cancer. Risk factors other than anovulation include nulliparity, hypertension, BMI >30 kg/m^2, and family history of endometrial cancer. As dysfunctional uterine bleeding is also a symptom of endometrial cancer, it is recommended that women with an increased risk for endometrial cancer and compatible symptomatology should be considered for endometrial biopsy. This is particularly important for women >45 years old, as the risk increases with age. Abnormal uterine bleeding not corrected after treatment should always be assessed for endometrial cancer.

21. What are the fertility treatment options for patients with PCOS?

Natural pregnancy is definitely possible in women with PCOS, as most women still have irregular ovulatory cycles. In women who are overweight or obese, lifestyle modifications and weight loss may be beneficial for the reestablishment of ovulatory cycles and increased fertility treatment efficiency, as well as improved pregnancy outcomes. However, many women will need ovulation induction with treatment options including letrozole, clomiphene citrate, metformin, and gonadotropins. Typical infertility investigation processes, such as testing the partner's sperm count, should be followed.

Letrozole (aromatase inhibitor) and clomiphene citrate (specific estrogen receptor modulator) both act by decreasing the feedback from estrogens at the hypothalamic level and promote FSH secretion and subsequent ovulation. Letrozole has a better efficacy and is considered the first-line treatment for ovulation induction.[1] Both increase the rates of pregnancy and live births in comparison to placebo and are indicated in women with PCOS and anovulatory infertility. They both increase the risk of multiple pregnancies (around 5%), and this risk is dose dependent.

Metformin is an alternative therapy for anovulatory infertility and has been shown to improve clinical pregnancy and live births, though at lower rates compared to letrozole or clomiphene. Metformin may be useful as an adjuvant therapy to other ovulation induction therapies, particularly in women with obesity, but literature supporting this is still limited.

Gonadotropins are a second-line therapy and must be managed by fertility specialists because they confer a risk of ovarian hyperstimulation syndrome and multiple pregnancies.

In vitro fertilization can be considered when ovulation induction therapy alone fails.

KEY POINTS

- Clinical signs and symptoms of PCOS include infrequent or irregular menses, infertility, hirsutism, acne, alopecia, and weight gain.
- PCOS is a diagnosis of exclusion, and other causes of irregular menses and hirsutism/acne need to be ruled out.
- PCOS is associated with many other conditions including type 2 diabetes, metabolic–associated steatotic liver disease fatty liver disease, hypertension, obstructive sleep apnea, and depression.
- All women with PCOS should be supported to make healthy lifestyle choices, regardless of weight.
- Pharmacotherapy can include estrogen therapy and/or insulin sensitizers, weight loss medications for those with obesity, and specific treatments for associated conditions and should be personalized to achieve the patient-specific treatment goals.

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CHAPTER 55

Hirsutism and Virilization

Tamis M. Bright

1. Define hirsutism.

Hirsutism is the excessive growth of terminal hair in androgen-dependent areas: upper lip, chin, sideburns, earlobes, tip of the nose, back, chest, areolae, axillae, lower abdomen, pubic triangle, and anterior thighs. Hirsutism affects 5–10% of females and is frequently associated with irregular menses and acne. Hirsutism should be distinguished from hypertrichosis, which is a non-androgen-dependent increase in vellus hair. Hirsutism can be quantified by using the modified Ferriman-Gallwey scoring system, which assigns a score for the amount of terminal hair growth in each of the nine androgen-dependent areas.

2. Define virilization.

Virilization refers to hirsutism, acne, and irregular menses, along with signs of masculinization that can include deepening of the voice, increased muscle mass, temporal balding, clitoromegaly, and increased libido. Virilization results from high circulating levels of androgens, close to or in the male range, and is usually caused by an androgen-secreting tumor.

3. Where are androgens produced?

Twenty-five percent of testosterone in women comes from the ovaries, 25% from the adrenal glands, and 50% from peripheral conversion of androstenedione, which is produced by both the ovaries and adrenals. Testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase, which is present in hair follicles, or to estradiol by the aromatase enzyme present in adipose tissue (Fig. 55.1). DHT binds to androgen receptors and is responsible for the transformation of vellus into terminal hair. Hair follicles also contain the enzymes that convert dehydroepiandrosterone (DHEA), which is produced by the adrenals, and androstenedione into testosterone.

4. What causes hirsutism?

Hirsutism is caused by hyperandrogenism. Androgens transform the fine, downy, minimally pigmented vellus hair in androgen-sensitive areas into coarse, pigmented, terminal hair. An increase in any of the androgenic steroids may cause high levels of DHT in the hair follicle and result in hirsutism.

Low levels of sex hormone–binding globulin (SHBG), which is produced by the liver, may promote hirsutism. Decreases in SHBG increase the free fraction of hormones available to androgen-sensitive hair. Hyperinsulinemia from insulin resistance, androgen excess, and hypothyroidism can decrease SHBG.

Increased activity of 5-alpha-reductase in the hair follicle, even with normal circulating androgen levels, also may cause hirsutism by the excessive conversion of testosterone into DHT and is referred to as *idiopathic hirsutism*.

5. List the conditions that result in hirsutism.

- Polycystic ovary syndrome (PCOS)
- Idiopathic or familial hirsutism
- Congenital adrenal hyperplasia (CAH)
- Cushing's syndrome
- Prolactinoma
- Hypothyroidism
- Acromegaly
- Medications

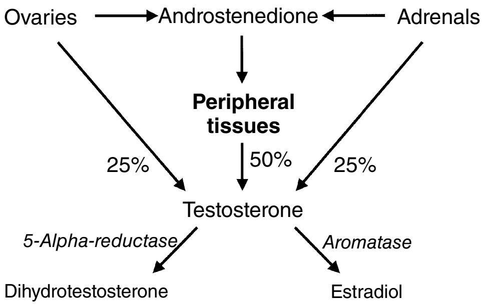

Fig. 55.1 Testosterone production and metabolism.

6. Describe the pathophysiology of PCOS.

The exact cause of PCOS is unknown, but insulin resistance, hyperandrogenism, and hypothalamic-pituitary dysfunction may all impact the pathophysiology of PCOS. Affected individuals have been shown to have an accelerated rate of pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. The gonadotropin secretory profile is highly dependent on the rate of GnRH pulsatility. Rapid GnRH pulses stimulate the secretion of luteinizing hormone (LH), but not follicle-stimulating hormone (FSH), from the pituitary gland. The increased LH/FSH secretory ratio results in arrested ovarian follicle development with cyst formation and hypertrophy of theca cells (hyperthecosis). This leads to constant estrogen and increased androgen production with chronic anovulation. High androgen levels also decrease the sensitivity of GnRH to the negative feedback from estrogen and progesterone contributing to the increased GnRH pulsatility. Most women with PCOS have insulin resistance, which augments the theca cell sensitivity to LH action contributing to hyperandrogenism. Consequently, a vicious circle is created, with insulin resistance leading to increased androgens; the increased androgens decrease the negative feedback of sex steroids on GnRH resulting in faster GnRH pulses; which in turn augment androgen production.

Genome-wide association studies (GWAS) have now identified a number of genetic targets linked to PCOS and insulin resistance.

7. How does PCOS manifest?

PCOS affects 10–13% of premenopausal women and manifests with symptoms of hyperandrogenism and anovulation. PCOS is the most common cause of hirsutism, resulting in about 70–80% of cases. Hirsutism is gradually progressive, usually beginning at puberty, and most women have irregular menses from the onset of menarche. However, in a study of women with hirsutism and regular menses, 50% had polycystic ovaries. Women with PCOS also frequently have insulin resistance and hyperinsulinemia. Because insulin decreases SHBG and the ovarian androgen response to LH stimulation, the hyperinsulinemia contributes to the elevated free androgen levels in PCOS. Thus, PCOS presents as a spectrum: some women have minimal findings, whereas others have the entire constellation of hirsutism, acne, obesity, infertility, amenorrhea or oligomenorrhea, male-pattern alopecia, acanthosis nigricans, hyperinsulinemia, and hyperlipidemia.

8. Describe the pathophysiology of idiopathic and familial hirsutism.

Idiopathic hirsutism is believed to be caused by increased cutaneous activity of 5-alpha-reductase or enhanced skin sensitivity to androgens. Familial hirsutism is an ethnic tendency to have a higher density of hair follicles per unit area of skin. Mediterranean populations and Hispanics have increased hair density, whereas Asians have lower density. Women with idiopathic or familial hirsutism usually have the onset of hirsutism shortly after puberty with a slow subsequent progression. They have a normal hormonal profile, including androgen levels, as well as normal menses and fertility.

9. Describe the pathophysiology of hyperandrogenism in CAH.

CAH results from a deficiency of one of the key enzymes in the cortisol biosynthesis pathway. Ninety percent of CAH is due to 21-hydroxylase deficiency, which causes a defect in the conversion of 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and of progesterone to

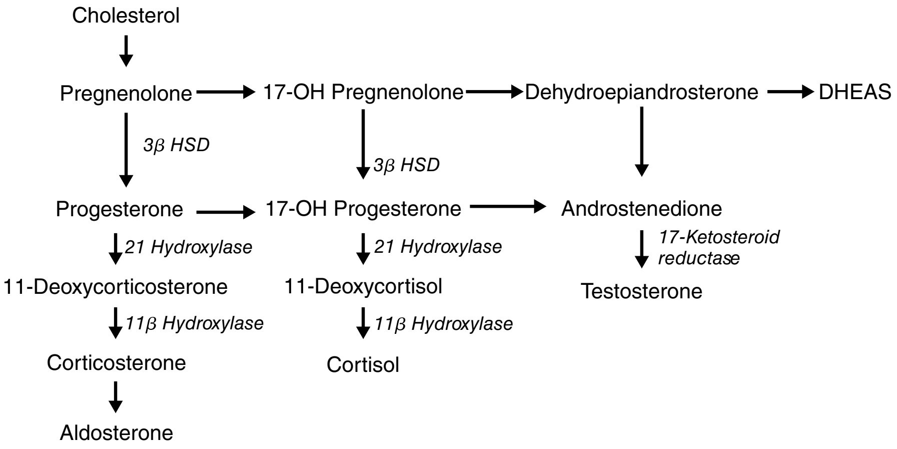

Fig. 55.2 Adrenal steroid biosynthesis. 3-beta-hydroxysteroid dehydrogenase (3 β HSD) dehydroepiandrosterone-sulfate (DHEAS).

deoxycorticosterone (DOC). The resulting low cortisol production rate leads to hypersecretion of pituitary adrenocorticotropic hormone (ACTH), which stimulates the overproduction of 17-OHP and progesterone as well as adrenal androgens, particularly androstenedione (Fig. 55.2). In its classic form, CAH causes adrenal insufficiency at birth and ambiguous genitalia in females. Women with CAH may develop hirsutism if they are inadequately treated or noncompliant with steroids. The late-onset or nonclassic type of CAH (NCCAH) results from milder deficiencies of the same enzyme, manifests later, and may cause childhood or postpubertal hirsutism in women.

10. Do any other causes of NCCAH result in hirsutism?

Other enzyme deficiencies besides 21-hydroxylase deficiency are extremely rare causes of NCCAH. Deficiency of 11-beta-hydroxylase decreases the conversion of 11-deoxycortisol to cortisol and of DOC to corticosterone. This stimulates hypersecretion of ACTH, with consequent overproduction of 11-deoxycortisol, DOC, and androstenedione. Women also frequently develop hypertension from the mineralocorticoid DOC.

A deficiency of 3-beta-hydroxysteroid dehydrogenase (3-beta-HSD) decreases the conversion of pregnenolone to progesterone and 17-hydroxypregnenolone to 17-OHP. This defect increases pregnenolone, 17-hydroxypregnenolone, and the androgens DHEA, DHEA sulfate (DHEAS), and androstenediol, which promote the development of hirsutism (see Fig. 55.2).

11. How do Cushing's syndrome, prolactinomas, hypothyroidism, and acromegaly cause hirsutism?

All causes of Cushing's syndrome may result in hypertrichosis because of increased vellus hair on the face, forehead, limbs, and trunk secondary to cortisol hypersecretion. Cushing's syndrome resulting from an adrenal tumor also may produce hirsutism and virilization from increased secretion of androgens with cortisol.

Hyperprolactinemia suppresses GnRH activity, which diminishes pulsatile LH secretion from the pituitary gland and results in decreased ovarian estrogen production and amenorrhea. Prolactin also increases the adrenal androgens, DHEA and DHEAS. The combination of low estrogen and increased androgens leads to hirsutism.

Hypothyroidism decreases SHBG and thereby leads to an increase in free testosterone. Acromegaly is frequently associated with PCOS, and the hirsutism may result from PCOS in conjunction with excessive insulin-like growth factor-1 (IGF-1), growth hormone, and insulin resistance.

12. Which medications can cause hirsutism?

Danazol, testosterone, glucocorticoids, metyrapone, phenothiazines, anabolic steroids, and valproic acid can cause hirsutism. Transference via skin contact of topical androgens used by a partner can cause hirsutism. Phenytoin, cyclosporine, diazoxide, minoxidil, glucocorticoids, streptomycin, penicillamine, and psoralens can cause hypertrichosis.

13. What conditions cause virilization?

Ovarian Disorders	*Adrenal Disorders*
Hyperthecosis	Congenital adrenal hyperplasia
Thecoma and Fibrothecoma	Adenoma
Granulosa and granulosa-theca cell tumors	Carcinoma
Arrhenoblastoma (Sertoli-Leydig cell tumors)	
Hilus cell tumors	
Adrenal rest tumors of the ovary	Other: anabolic steroids
Luteoma of pregnancy	

14. When should a woman be evaluated for hirsutism?

Any woman with moderate-to-severe hirsutism or an increased Ferriman-Gallwey score, rapid development of hirsutism, or coexistence of amenorrhea, irregular menses, infertility, acanthosis, or virilization should be evaluated. A woman with regular menses who shows significant distress over her hirsutism also may warrant a workup.

15. What information is important in the history?

- Age at onset, progression, and extent of hair growth
- Current measures of hair removal and frequency of use
- Age at menarche, regularity of menses, and fertility
- Family history of hirsutism
- Change in libido or change in voice
- Symptoms of Cushing's syndrome, prolactinoma, acromegaly, or hypothyroidism
- Medications, anabolic steroid use, partner's use of topical androgens

16. What findings are important on physical examination?

- Distribution and degree of hirsutism
- Increased muscle mass, temporal balding, clitoromegaly, or acne
- Obesity
- Acanthosis nigricans
- Visual field defects
- Moon facies, plethora, buffalo hump, supraclavicular fat pads, striae, or thin skin
- Galactorrhea
- Goiter, loss of lateral eyebrows, periorbital edema, dry skin, or delayed reflexes
- Acromegalic features
- Abdominal or pelvic masses

17. What laboratory tests should be ordered for a patient with hirsutism?

Laboratory testing should be guided by the results of the history and physical examination. Most authors advocate against testing in women with regular menses and only gradual progression of mild hirsutism. Serum levels of total and free testosterone, SHBG, DHEAS, and 17-OHP can be useful tests, depending on the individual patient. Recent guidelines recommend initial screening with total testosterone by liquid chromatography-tandem mass spectrometry (LC–MS/MS) followed by a free testosterone level if the total testosterone is normal. DHEAS and 17-OHP are measured only in those women with high total or free testosterone to determine the etiology of hyperandrogenism. If a woman is from a high-risk ethnic group for NCCAH, then a 17-OHP can be obtained even with normal androgen levels. Women with signs or symptoms of hypothyroidism, hyperprolactinemia, acromegaly, or Cushing's syndrome also should be evaluated with serum thyroid-stimulating hormone (TSH), prolactin, insulin-like growth factor-1 (IGF-1), or Cushing's screening (24-hour urine cortisol, late-night salivary cortisol, or a 1-mg overnight dexamethasone test), respectively. Otherwise, these tests need not be obtained in every patient.

18. How are the results of these laboratory tests interpreted?

For a woman without signs of virilization, it is important to differentiate idiopathic hirsutism, PCOS, and NCCAH, because each is treated differently. Idiopathic hirsutism has normal levels of both total and free testosterone. PCOS has high-normal or increased total and/or free testosterone, normal or slightly increased DHEAS, and normal 17-OHP. NCCAH has elevated testosterone and DHEAS and mild-to-marked elevation of 17-OHP. An early-morning follicular phase level (random morning if amenorrheic) of 17-OHP >1000 ng/dL confirms NCCAH. A level of 200–1000 ng/dL is strongly suggestive of NCCAH and should be confirmed with an ACTH stimulation test. NCCAH is confirmed if the 60-minute 17-OHP value after 250 mcg of ACTH is >1000 ng/dL. (See Chapter 38 on Congenital Adrenal Hyperplasia for additional discussion on this issue.)

19. What tests should be ordered in a woman with virilization?

After excluding anabolic steroid abuse as an etiology, a woman with virilization should be evaluated to determine whether she has an adrenal tumor, NCCAH, an ovarian tumor, or hyperthecosis, which is due to androgen producing nests of luteinized theca cells in the ovaries. Tests should include serum total testosterone, DHEAS, and 17-OHP. A markedly increased testosterone level, usually in the adult male range, with normal values on the other tests points to an ovarian tumor or hyperthecosis. High levels of DHEAS (>700 ng/mL) with or without high testosterone levels suggest an adrenal tumor. Increased levels of 17-OHP with modest elevations of DHEAS and testosterone are more consistent with NCCAH and can be confirmed, as above, with an ACTH stimulation test. Laboratory values suggesting ovarian tumors or hyperthecosis should be followed with transvaginal ultrasonography (preferred) or computed tomography (CT) of the ovaries. Treatment is usually unilateral oophorectomy for tumors or bilateral for hyperthecosis in postmenopausal women or GnRH agonists for hyperthecosis in premenopausal women. An adrenal CT should be done for values consistent with adrenal tumors. If no mass is found, 18F fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) or venous sampling of the ovarian or adrenal veins can be performed for localization before surgical removal.

20. How is hirsutism treated?

For premenopausal women not desiring pregnancy, the most common treatment is oral contraceptive pills (OCPs). Antiandrogens can also be prescribed in addition to OCPs or alone if another form of reliable contraception is utilized or in postmenopausal women. Multiple different cosmetic measures are effective and are often used in conjunction with OCPs and antiandrogens. For women who desire fertility, only cosmetic measures are safe.

For women with PCOS, weight reduction should also be encouraged; this usually improves insulin resistance and SHBG levels, may help regulate menses, and may resolve anovulation. GnRH agonists have been tried in severe cases when other modalities have not been effective. Women with PCOS should also be evaluated for glucose intolerance, diabetes, and hyperlipidemia because of their high prevalence in this disorder. These problems should be addressed separately because they are not resolved by treating hyperandrogenism alone.

If women with NCCAH do not have improvement of their hirsutism with the above measures, prednisone 4–6 mg or dexamethasone 0.25–0.5 mg at night will frequently decrease androgen levels to normal. The medication can then be tapered to the lowest effective dose, with monitoring for any adverse effects of glucocorticoid therapy.

21. Describe how OCPs are used for the treatment of hirsutism.

OCPs are the most commonly used therapy for hirsutism. The progestin decreases LH and thereby decreases androgen production, and the estrogens increase SHBG, which further decreases free testosterone levels. OCPs also decrease the risk of endometrial hyperplasia in women with amenorrhea or oligomenorrhea. Monophasic and triphasic preparations work equally well. Studies with preparations containing the more androgenic progestin levonorgestrel had similar effects on hirsutism as the less androgenic progestins. Low-dose estrogen (20 mcg) OCPs also were shown to have the same effect as higher-dose estrogen OCPs.

Potential side effects include weight gain, bloating, nausea, emotional lability, breast pain, and venous thromboembolism (VTE). Low-dose estrogen OCPs have less risk of VTE. OCPs containing levonorgestrel, norgestimate, or norethindrone have a lower risk of VTE compared with those containing other progestins.

22. Describe how antiandrogens are used for the treatment of hirsutism.

Spironolactone is an androgen receptor blocker that also inhibits 5-alpha-reductase. Side effects include diuresis, fatigue, hyperkalemia, and dysfunctional uterine bleeding. Doses are 50–100 mg twice daily. Finasteride, a 5-alpha-reductase inhibitor, effectively decreases hirsutism at dosages of 2.5–7.5 mg/day. Side effects are minimal. Flutamide, another androgen receptor blocker, has similar effectiveness as the other antiandrogens but has been associated with rare fatal hepatotoxicity and, therefore, is not recommended. The antiandrogens are usually used in combination with OCPs for additive effects and to give adequate birth control because antiandrogens can feminize a male fetus. If the woman is not on OCPs, then another form of reliable birth control needs to be utilized.

23. Describe how GnRH agonists are used for the treatment of hirsutism.

By providing constant rather than pulsatile GnRH levels to the pituitary, GnRH agonists reduce gonadotropin secretion and thereby decrease ovarian production of both estrogen and androgen. Estrogen replacement must be given to avoid hot flashes, vaginal dryness, and bone density loss. Leuprolide (3.75 mg per month intramuscularly), nafarelin nasal spray, and goserelin subcutaneous implants have been utilized. Some studies demonstrated an increased effect over OCPs alone, whereas others showed similar effects. The preparations are expensive and, thus, are usually reserved for women with severe PCOS unresponsive to other therapies.

24. What topical agent is approved for the treatment of hirsutism?

Eflornithine hydrochloride 13.9% cream applied twice daily is used for the treatment of facial hirsutism. Eflornithine irreversibly inhibits ornithine decarboxylase, an enzyme necessary for hair follicle cell division. Inhibition of ornithine decarboxylase results in a decreased rate of hair growth; improvement in hirsutism can be seen by 6–8 weeks of use. The most common side effects are pseudofolliculitis barbae, burning, tingling, erythema, dry skin, or rash over the applied area. Generally, side effects resolve without treatment and rarely require discontinuation of the medication. The hirsutism will return to baseline by 8 weeks after discontinuation of the medication.

25. What cosmetic measures can be used for the treatment of hirsutism?

Shaving, plucking, waxing, and chemical depilating are effective measures that can be used to temporarily remove terminal hair. Bleaching can also make hair less apparent. These measures can be used alone or in combination while the woman waits for medications to decrease new growth and rate of transformation into terminal hair. Electrolysis, either through thermolysis or direct current, is a permanent method of hair removal but can be painful.

Photoepilation using ruby, alexandrite, diode, or yttrium aluminum garnet lasers, or intense pulsed light therapy, is an effective treatment for hirsutism. At least three to six treatments about 4–6 weeks apart are required. The techniques result in the removal of hair through thermal injury to the hair follicle with a period of usually 6 months before regrowth of hair, which is then thinner and lighter. Women with light skin and dark hair have the best results with the fewest side effects. The side effects include minimal discomfort, local edema, erythema lasting 24–48 hours, burns, and infrequent hypo- or hyperpigmentation. A very rare side effect of laser treatment is paradoxical hirsutism, which is increased hair growth instead of removal.

26. How do you choose the appropriate therapy for the woman's hirsutism?

Most women are given a trial of OCPs for 6 months and are advised to use cosmetic measures while waiting for the medication to work. If needed, an antiandrogen can then be added. Topical eflornithine may be used alone or in combination with the other measures. Because of their more serious side effects and/or higher cost, the other medications are reserved for the most severe cases where OCPs and antiandrogens fail. No matter what therapy is chosen, the woman must be made aware that results will not be seen for at least 3–6 months. Although many medications have been used, only topical eflornithine is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of hirsutism. Unfortunately, most women have a relapse of hirsutism approximately 12 months after discontinuation of medical therapy.

KEY POINTS

Hirsutism and Virilization

- Hirsutism is the excessive growth of terminal hair and is frequently associated with irregular menses.
- Virilization consists of hirsutism and irregular menses associated with signs of masculinization.
- Hirsutism and virilization usually result from excess androgens.
- The common causes of hirsutism are polycystic ovary syndrome, NCCAH, idiopathic or familial hirsutism, and medications.
- The common causes of virilization are ovarian tumors, ovarian hyperthecosis, adrenal tumors, and CAH.

KEY POINTS

Diagnosis and Treatment of Hirsutism and Virilization

- Appropriate laboratory testing includes at least a serum total testosterone, followed by free testosterone, dehydroepiandrosterone sulfate, and 17-hydroxyprogesterone in select women.
- Treatment of hirsutism is usually with oral contraceptive pills, frequently in combination with an antiandrogen or eflornithine in addition to cosmetic measures.
- Treatment of virilization is surgical removal of the tumor or steroid treatment for congenital adrenal hyperplasia.

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Menopause

Wesley Nuffer and Deborah N. Gallegos

1. Define menopause.

The formal definition of menopause is the permanent cessation of menses, clinically defined as 12 months after the last menstrual period. It marks the end of a woman's normal ovarian function.

2. When does menopause usually occur?

Women generally experience menopause between 45–55 years of age, with the median age for the last menses being 51.4. There is large variability in the exact age for menopause to occur. Women who are underweight or who smoke tend to have an earlier menopause, while overweight women may experience a later menopause. There appears to be a genetic component involved, as women often will experience menopause around the same time as their mother or sister, but this does not always hold true. It also appears that women in Asia may experience menopause at an earlier age.

3. How is menopause diagnosed clinically?

In a woman who is over 45 years old, 12 months of secondary amenorrhea (no cycles) is sufficient to diagnose menopause. While a pelvic exam may reflect some atrophy of the vaginal mucosa, this is not always remarkable. There are usually elevations of both follicle-stimulating hormone (FSH), which rises significantly (approximately 10-20 fold), and luteinizing hormone (LH), which has a more modest rise (approximately 3-fold). It is generally considered that an FSH level above 40 IU/L indicates ovarian failure, but these levels are not reliable for diagnosis, as there are circumstances when these hormones may be elevated prior to menopause. FSH levels are generally evaluated in women younger than 45 with menopausal symptoms.

4. What is perimenopause?

Menopause should not be thought of as naturally occurring suddenly, but rather as a transitional process over time. Perimenopause (also called the menopause transition) describes the transition toward menopause, when cycles can vary in frequency and severity. This period of time lasts approximately 4 to 8 years. Menopause symptoms often begin to appear during this time.

5. Physiologically, what determines the timing of menopause?

Loss of ovarian follicular function results in the absence of ovarian oocytes, which signals the cessation of menstruation in women. Oocyte numbers decline throughout a woman's life, actually peaking in number in utero and declining quite rapidly before birth, when approximately 80% of oocytes have been lost. Eventual exhaustion of most or all oocytes causes menses to cease.

6. What is primary ovarian insufficiency?

Primary ovarian insufficiency (previously called premature ovarian insufficiency) occurs when the ovaries stop functioning before the age of 40. Symptoms are very similar to those experienced by women entering menopause, but there are differences, as these women can have irregular or occasional periods for years, and may even become pregnant. There can be several causes of this condition, including autoimmune disorders, chromosomal defects, chemotherapy treatment, and some unknown causes. The incidence of primary ovarian insufficiency is estimated to be approximately 1% of women in the United States.

7. What are the symptoms of menopause?

The hallmark symptom of menopause, which often occurs during the perimenopause transition, is recurrent hot flashes, medically called *vasomotor symptoms*. These are episodes that last seconds to minutes during which a woman experiences a tremendous warming of her body, often with accompanying redness of the skin and sweat production. Menopausal women often describe this variable temperature control as occurring at night, coined "night sweats." Other symptoms that are less prevalent can include insomnia, short-term memory loss or "mental fogginess," vaginal dryness, low libido, weight gain and slow metabolism, and a loss of "youthfulness" to the skin, hair, and nails.

8. Will all women experience menopause symptoms?

It is estimated that the majority of women (approximately 85%) will experience some type of vasomotor symptoms with menopause. This can vary greatly in severity, with the most severe symptoms usually occurring in women who have had their ovaries surgically removed, thereby transitioning to what has been called "instant menopause." Roughly 25% of women describe their menopause symptoms as severe.

9. Do menopausal symptoms last indefinitely?

Generally, menopausal symptoms are most prominent during perimenopause or the first few years after menopause. Most women are able to tolerate these symptoms better after 3–5 years. Approximately 80% of women report resolution of their vasomotor symptoms after 5 years. However, some women continue to suffer from hot flashes and other menopause symptoms 10 years or longer after menopause, at almost the same severity as when they first appeared.

10. What other physiologic changes accompany menopause?

There are a number of physiologic changes that happen during the menopause transition. Tissue changes occur in the ovaries and vagina, with a loss of vaginal mucosa, leading to atrophy and often increased vaginal dryness. Decreased estrogen alters the balance between bone-building cells (osteoblasts) and bone resorption (osteoclasts), which results in bone loss after menopause. The blood vessels lose some elasticity, and there are alterations in the lipid profile (mainly increased triglycerides and LDL cholesterol and decreased HDL cholesterol), which can lead to increased risks of cardiovascular disease.

11. What estrogen(s) are present in a woman's body?

Women naturally have three distinct estrogens present in varying amounts: estrone (E1), estradiol (E2), and estriol (E3). E2 is the most potent of these; it binds equally to both the α and β estrogen receptors and converts freely back and forth with E1 in the body. E2 is also the primary estrogen during the reproductive years, being produced by the ovaries. There is some evidence to suggest that E1 has a higher carcinogenic risk compared with the other estrogens, possibly due to its higher affinity for the α-estrogen receptor (approximately 5:1 α:β). E1 becomes the primary estrogen after menopause, formed in the adipose tissue from androstenedione, which is secreted by the adrenal glands. E3 is a metabolite of E2 and E1 and will not convert back to E1 or E2 once formed, but rather is excreted through the urine. It has a higher selective binding to the β-estrogen receptor (3:1 β:α). E3 is the primary estrogen during pregnancy. There is a fourth estrogen (estetrol or E4) that is produced only during pregnancy, reaching the maternal circulation through the placenta.

12. There was a major shift in managing symptomatic menopause after the Women's Health Initiative (WHI) trial. Why did this occur?

The WHI trial was a landmark study from the National Institute of Health (NIH) that enrolled over 27,000 women aged 50–79. Those women with no previous hysterectomy received combined conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) or placebo (16,608 women) and those women with a previous hysterectomy received either CEE or placebo (10,739 women). The primary outcome of this trial was coronary heart disease events. Much of the media attention toward this trial came when the combined arm of CEE and MPA was stopped early in July 2002 after investigators found that the associated health risks outweighed the potential benefits of therapy. Data showed an increased risk of invasive breast cancer, along with increased incidence of coronary heart disease, pulmonary embolism, and stroke. Positive outcomes included a reduction in colon cancer and fewer hip fractures. The estrogen-alone arm also showed an increased risk of stroke and blood clots without preventing heart disease.

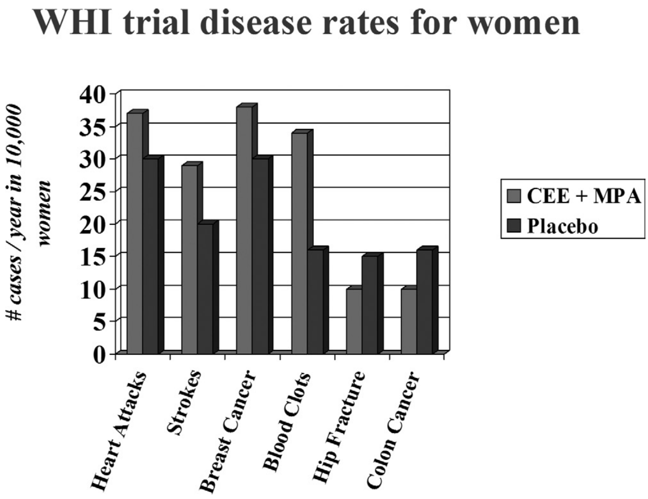

Fig. 56.1 WHI trial results.

13. What are some of the limitations of the WHI trial data?

One of the largest recognized limitations to these data is the age of women at enrollment; it is widely believed that a woman's greatest benefit derived from hormone replacement therapy (HRT) occurs in the years just following menopause, or in the age range of 50–60. The WHI enrolled women aged 50–79 years (average age = 63.2) including a large number of women over age 60, which may have impacted the trial results. The majority of women in the trial were also overweight (average BMI of 28.5 kg/m^2), which may have increased their risk of heart disease and cancer. There were also a fair number of women who dropped out of the study. Furthermore, only one hormone dose and type (CEE 0.625 mg/d plus MPA 2.5 mg/d or CEE 0.625 mg/d alone) was used in the trial, so the rationale of extrapolating these results to state that all hormone products carry the same risk has been questioned.

14. What do national organizations say regarding hormone replacement in menopausal women?

Overall, there is a strong consensus across major organizations regarding the role of HRT in menopause. Both the American College of Obstetrics and Gynecology (ACOG) and the North American Menopause Society (NAMS) recommend estrogen and possible progestagen therapy only for symptomatic relief and recommend that women should be on the lowest dose possible for the shortest amount of time. Similarly, The American Association of Clinical Endocrinologists (AACE) clinical guidelines recommend against long-term HRT and that it not be used for cardiovascular disease prevention. Estrogen is indicated for osteoporosis prevention, but risks of long-term use are thought to outweigh the benefits, so this indication is generally reserved for women <60 years and should be carefully evaluated based on the individual's risk and possible use of other osteoporosis medications. While HRT should not be used for cardiovascular protection, current evidence suggests that HRT during early menopause does not increase heart disease risk. The decision on whether a woman should be treated for severe symptoms should be an individual one made in collaboration between the patient and the provider. Perceived risks based on the WHI trial and accompanying literature should be presented and weighed against the severity of symptoms and the woman's health-related quality of life. Since the greatest benefits of HRT therapy are seen in women <60 years old, it is generally thought that any HRT use should occur between ages 50–60, and attempts should be made to taper the therapy to discontinuation every 3–5 years.

15. Are there other therapies available for managing menopausal symptoms?

Based on the nature and severity of symptoms, there are a variety of other approaches for menopause symptom management without HRT. Antidepressant drugs, such as fluoxetine, paroxetine, and venlafaxine, have documented evidence for benefit in managing hot flash symptoms. A new class of medications called *Neurokinin 3 receptor antagonists* are beginning to be explored for menopause treatments. The first of these, fezolinetant (Veozah), has been approved by the FDA for use in controlling vasomotor symptoms. These drugs block neurokinin B, a chemical that has been linked to hot flashes. There is early evidence for increased quality of life and decreased hot flashes and night sweats with use. This medication is associated with higher costs (over $600 monthly), and insurance coverage may vary. There are also herbal products, such as soy derivatives and black cohosh, for which questionable success has been documented by virtue of relatively weak phytoestrogen activity. Behavioral and complementary interventions, including hypnosis, have been evaluated and shown to have some benefits in mild-moderate symptom control. NAMS put out a position statement in 2023 stating that supplements, herbal remedies, and soy products/foods are generally not recommended for this use. Alternate recommendations, with higher levels of evidence from NAMS, include fezolinetant, cognitive-behavioral therapy, some antidepressants, gabapentin, and oxybutynin.

16. Does the route of administration matter when it comes to hormone replacement therapy?

Transdermal hormone administration produces different effects than those when taking the same hormones orally because it avoids the “first pass effect” where the liver metabolizes the hormones and can produce partially active or inactive metabolites. There are several prescription hormone preparations available for delivery by patch or in a cream. AACE guidelines recognize that transdermal estrogen may theoretically reduce the risk of thromboembolic disease. Likewise, oral progesterone is metabolized extensively, and some of the by-products can be extremely sedating, so administering progesterone by the transdermal route can allow for lower doses with less sedation side effects. Topical administration is also valuable for symptoms such as vaginal dryness, where a woman can relieve localized symptoms by applying the product vaginally with less systemic absorption. Generally, topical hormone formulations come in lower doses than their oral counterparts. Some of the hormones compounded by pharmacies are prepared as a sublingual lozenge or drop, to be placed or dissolved under the tongue. These, too, absorb directly into the bloodstream, avoiding the oral-intestinal-hepatic route.

17. What is a bioidentical hormone?

The term *bioidentical* was coined to represent hormones that are identical to what the body naturally produces, usually from plant-derived sources. While bioidentical hormones are often promoted by compounding pharmacies, many of the FDA-approved prescription hormone products, such as estradiol and progesterone, are also bioidentical. This term has been used to contrast these from other hormone products, most notably CEE, which originates from pregnant mare urine, and MPA, a synthetic progestagen compound. Many agencies, such as the FDA, ACOG, and the Endocrine Society, consider “bioidentical” to be a marketing term, not one based on scientific evidence. Today, there are a number of FDA-approved hormone products that are bioidentical, such as micronized progesterone (Prometrium), estradiol, and a combination of estradiol and progesterone (Bijuva). Compounding pharmacies also compound bioidentical hormones, but national organizations have expressed concerns regarding a lack of regulation and official labeling of these products.

18. Are bioidentical hormones safer for supplementation?

There has been a tremendous amount of publicity and promotion of compounded bioidentical hormones following the WHI trial as women sought other options for controlling severe menopause symptoms. Currently, the majority of the evidence suggests that all estrogen products are similar in nature and effects, regardless of source. Proponents of bioidentical hormones argue that the physiologic similarity of these molecules yields benefits that are not seen with other estrogen and progestagen hormones. Some compounded hormones include E3, which is not FDA approved for use in the United States, although it is used in Europe and other countries. In regards to bioidentical progesterone, there are some data to support different physiologic activities when compared to MPA and other synthetic progestins. Evidence from observational trials and controlled primate trials suggest a better safety profile than MPA, but large randomized placebo-controlled trials are still lacking to verify this potential benefit.

19. If a woman is on HRT, should dosing be based on serum or saliva levels?

According to AACE guidelines, HRT should be based on symptoms, not on specific drug or hormone levels. There is no current evidence showing that hormone levels in saliva are biologically meaningful. Saliva test proponents cite that hormones are generally lipophilic, and that active hormones are not reliably measured in the blood while saliva levels more closely represent intracellular hormone levels. Saliva levels, however, are documented to vary substantially, depending on the time of day when they are collected, and have not been established as a reliable indicator of therapeutic response. Their assays are not FDA-approved and generally not considered to correlate with serum hormone levels. It is also often difficult for women to obtain coverage of payment for saliva levels through their medical benefits, and the cost can be significant. Blood levels of hormones can be used to assess how high a medication or supplement may boost the hormone, but they should not be used to determine treatment response. It is recommended not to titrate medication therapy to any serum, saliva, or urinary value. The patient should be treated with the lowest possible doses of hormones to adequately control menopausal symptoms.

20. What is the role of progestogen supplementation?

Progestogens, most notably MPA, are used in conjunction with estrogen treatment to protect women from developing endometrial cancer. They are given to women who have not had a hysterectomy. There is a suggestion, based on small studies, that progesterone supplementation may yield additional benefits, even in women who have had a hysterectomy, but it is not routinely recommended for use beyond endometrial protection.

21. Do women need androgen supplementation?

This is a controversial area. The Endocrine Society's consensus statement recommends against a diagnosis of androgen deficiency in women, citing a lack of data documenting what "normal" androgen levels are in women across their life span. Several randomized control trials have demonstrated that for women experiencing hypoactive sexual desire disorder, prescribing testosterone at low, physiologic levels has proven to be safe and effective. Transdermal preparations are generally preferred, with testosterone levels monitored before and during treatment. Continuation of treatment should be based not on levels but on clinical response. When supplemented, dosing is often limited by unwanted side effects (oily skin and acne, hirsutism, voice lowering).

22. Does male menopause exist?

Androgen levels decline with age in men and there are indications for supplementation in some circumstances. This is not considered "male menopause," primarily because it does not appear to be a physiologically programmed event.

23. What are some good menopause/HRT references?

- MenoPro- A mobile app for women bothered by menopause symptoms, sponsored by NAMS.
- American Association of Clinical Endocrinologists Position Statement on Menopause-2017 Update: Endocr Pract. 2017 Jul;23(7):869-880. doi: 10.4158/EP171828.PS.
- North American Menopause Society Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. *J North American Menopause Society* 2017, 24 (7): 728-753.
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KEY POINTS

Menopause

- Menopause is the cessation of menses, comprising approximately the last third of a woman's life.
- Menopausal symptoms are most severe early during perimenopause and menopause, with the hallmark symptom being hot flashes.
- Hormone replacement therapy should be reserved primarily for symptomatic relief, targeting women aged 50–60, using the lowest doses for the shortest interval of time.
- The term *bioidentical* is largely considered a marketing term but refers to any hormone identical to what is found in the body and includes both prescription hormones (i.e., estradiol, progesterone) as well as compounded products.
- Hormone therapy should be based on symptom control, not on blood or saliva hormone levels.

KEY POINTS: KEY WORDS

- Hot flashes
- Bioidentical
- Progestogen
- Oocyte
- menopause
- hormone replacement

WEBSITES

www.acog.org
www.menopause.org

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Gender-Affirming Care for Transgender and Gender-Diverse Adults

Micol S. Rothman and Sean J. Iwamoto

1. What is gender identity?

Gender identity refers to a person's innate, self-identified gender (e.g., as a man, a woman, nonbinary, or something else) that may or may not align with their external genitalia or sex recorded at birth. Gender identity is not visible to other people.

2. What is the difference between gender incongruence and gender dysphoria?

Gender incongruence is defined as a person's gender identity and/or gender expression differing from their sex recorded at birth or what is typically associated with the designated gender. Not everyone with gender incongruence has gender dysphoria or seeks gender-affirming care. In the updated 11th edition of the International Statistical Classification of Diseases and Related Health Problems (also known as ICD-11), gender incongruence was moved out of the "Mental and Behavioral Disorders" chapter and into the new "Conditions Related to Sexual Health" chapter to destigmatize the transgender-related experience.

Gender dysphoria refers to the distress and unease associated with gender incongruence. See Table 57.1, for other terminology.

Society and the medical literature are continually evolving when it comes to transgender and gender-diverse (TGD) terminology. Although the above-mentioned list is not exhaustive, it represents some of the current terms used in practice. There has been a shift away from using "male-to-female" (or the abbreviation "MTF") to represent transgender women/transfeminine people and "female-to-male" (or the abbreviation "FTM") to represent transgender men/transmasculine people, although one may still see or hear these terms.

It is important to be aware that sex recorded at birth, gender identity, and gender expression are not identical or interchangeable. Knowing someone's gender identity, which may or may not fall into the traditional gender binary of male or female, does not tell you the person's sexual orientation, sexual behavior, or sexual attraction. Make no assumptions, and always ask patients for the names and pronouns they use.

3. How many transgender and gender-diverse people live in the United States?

It has historically been difficult to assess the prevalence of TGD identity in the population because it requires self-identification. The 2022 Williams Institute study estimated there were 1.6 million adults and youth who identified themselves as TGD (approximately 0.5% and 1.4% of the adult and youth populations, respectively). Limitations remain in relation to self-reporting and the terminology used, as noted above. Other studies have suggested a higher prevalence of gender dysphoria among the US veteran population compared to the general population and among survey-based studies compared to health systems-based studies.

4. Why is it important for endocrinologists to be trained in transgender and gender-diverse medicine?

Although awareness of gender diversity has increased substantially in the last decade, barriers continue to exist in healthcare for TGD individuals. In the 2022 United States Transgender Survey, with over 90,000 respondents from all 50 states, 28% of individuals reported not seeing a doctor when they needed to in the last 12 months due to cost and 24% stated they did not seek care because of fears of mistreatment. Creating a welcoming environment for people includes, but is not limited to, provider and staff education, identifying and using patients' names and pronouns, being mindful of protected health information on paper and electronic forms, and establishing gender-neutral facilities.

With their detailed knowledge of hormone physiology and management, endocrinologists are uniquely positioned to provide gender-affirming hormone therapy (GAHT) to TGD people.

TABLE 57.1 Terminology

TERM/PHRASE	DEFINITION
Cisgender	A person whose gender identity and gender expression align with their sex assigned at birth (i.e., not transgender; e.g., cis women, cis men). Avoid using the term “normal” when referring to cisgender people.
Gender expression	The external manifestations of a person’s gender. May or may not conform to the socially defined behaviors and external characteristics that are historically referred to as *masculine* or *feminine* (e.g., clothing, haircut, jewelry, social interactions, speech patterns)
Nonbinary, gender fluid, pangender, polygender (potentially other terms to describe gender diversity)	People who may identify and present themselves as both or alternatively male and female, as neither male nor female, or as a gender outside the male/female binary.
Sex recorded at birth	Refers to sex recorded at birth typically based on genitalia (e.g., male, female, or intersex).
Sexual orientation	The physical, romantic, emotional, and/or spiritual attraction a person has for another person (e.g., lesbian, gay, heterosexual, bisexual, pansexual, polysexual, or asexual)
Transgender	Encompasses people whose gender identity and/or gender expression differs from their sex assigned at birth; independent of the decision whether to use gender-affirming hormones or undergo surgery. The term “transgendered” or “transgender” should not be used.
Trans man/Trans male/Transmasculine	Generally refers to a person who was assigned female at birth and whose gender identity and/or gender expression is male/masculine.
Trans woman/Trans female/Transfeminine	Generally refers to a person who was assigned male at birth and whose gender identity and/or gender expression is female/feminine.

A 2023 US survey of endocrinologists who prescribe GAHT found that over 30% of respondents provide GAHT to more than 100 TGD patients and over 30% have been prescribing GAHT for more than 15 years. Results also revealed that over 40% of respondents still require documentation of a psychosocial evaluation from a mental health professional before initiating GAHT. The 2017 Endocrine Society Clinical Practice Guidelines advise that trained mental health providers diagnose gender dysphoria/gender incongruence in adults seeking GAHT. On the other hand, the 2022 World Professional Association for Transgender Health (WPATH) Standards of Care, version 8, recommends that any health care professional can evaluate TGD patients for gender dysphoria/gender incongruence. More research is needed on the impact of psychosocial evaluations on patients prior to GAHT initiation and best practices for aligning clinical practice with guideline recommendations.

5. What medical and mental health disparities are observed in transgender and gender-diverse people?

Medical and mental health disparities exist between TGD and *cisgender* (denoting or relating to a person whose sense of personal identity and gender corresponds with their sex recorded at birth) people. A case-control study utilizing the 9th edition of the International Statistical Classification of Diseases and Related Health Problems–Clinical Modification (ICD-9–CM) codes for “transgender” identification of US veterans between 1996 and 2013 revealed statistically significant disparities among TGD veterans regarding depression, suicidality, posttraumatic stress disorder, eating disorders, and other mental health conditions compared with cisgender veterans. TGD veterans also had a higher likelihood of human immunodeficiency virus (HIV), cardiac arrest, cerebral vascular disease, congestive heart failure, diabetes, hypercholesterolemia, hypertension, ischemic heart disease, obesity, and other medical conditions compared to cisgender veterans. A 2023 study specifically looking at older veterans aged ≥65 years, found significant disparities in social stressors (e.g., social/family problems, lack of access to care/transportation, violence, and military sexual trauma) and health conditions (e.g., depression, Alzheimer's disease, and cancer) among older TGD veterans compared to older cisgender veterans. Interestingly, older TGD veterans had a lower likelihood of substance abuse and anxiety compared to older cisgender veterans.

A 2021 study analyzing the TransPop US Transgender Population Health Survey compared responses from 271 TGD (nearly 50% aged 18–29 years) and 1162 cisgender respondents (about 20% aged 18–29 years). TGD respondents were more likely to rate their health as fair/poor and self-reported a higher prevalence of HIV, emphysema, sleep disturbances, and ulcers, compared to cisgender respondents. TGD respondents also reported a lower prevalence of high cholesterol and diabetes compared to cisgender respondents.

6. What are the recommended criteria for initiating GAHT in adults?

The 2017 Endocrine Society Clinical Practice Guidelines criteria for GAHT include persistent gender dysphoria/gender incongruence, the capacity to make a fully informed decision and to consent for treatment, the age of majority, and mental health concerns, if present, must be reasonably well controlled. The 2022 WPATH Standards of Care, version 8, criteria are similar: gender incongruence is marked and sustained (and meets diagnostic criteria for gender incongruence prior to hormone initiation, where required), demonstrates the capacity to consent for treatment, other possible causes of apparent gender incongruence have been identified and excluded, the person understands the effect of GAHT on reproduction and reproductive options have been explored. However, the language regarding mental health changed to state that physical conditions that could negatively impact the outcome of GAHT have been assessed. This is based on findings that have shown decreases in anxiety, depression, and suicidal ideation in TGD patients after GAHT initiation and that these conditions are not considered contraindications to GAHT.

The role of the mental health provider has evolved in recent guidelines. Although previously it was required that patients seek a diagnostic evaluation and a letter from a mental health professional prior to GAHT initiation, the 2017 Endocrine Society and WPATH Standards of Care, version 8, guidelines specify that any health care professional with competencies and expertise in assessing TGD people can make this diagnosis (if required in that location). In some "informed consent" models, the medical provider makes the assessment and diagnosis and then assesses the capacity of the person to provide consent for GAHT. Some providers and clinics require a signed informed consent form, whereas others document their informed discussions and patient understanding in the chart.

In our integrated transgender health clinic, we offer the opportunity to see a mental health provider as we have seen that there are also stressors that occur related to gender transition, as in any life change, and the mental health provider on the team can play a valuable role in providing additional support during this time.

7. What are the options for feminizing GAHT?

For most patients with gender incongruence or gender dysphoria pursuing feminizing GAHT, estrogen is the main hormonal therapy. It can be administered via oral (e.g., 17-β-estradiol), transdermal, or intramuscular (e.g., estradiol valerate or cypionate) routes. Studies have not yet demonstrated that one route of administration is "better" than the others in terms of feminizing effects, as patients can have different priorities for physical changes. See Question 20 about the 2022 WPATH guidelines recommending the use of transdermal estrogen in transgender women aged ≥45 years to mitigate VTE risk. Although not listed in the guidelines as a route of administration, some people inject estradiol subcutaneously (SQ), and a few studies have shown that dosages and levels are similar to intramuscular (IM) injections. Injections still carry the risk of achieving potentially harmful supraphysiologic serum estradiol levels, even at lower doses than recommended in the guidelines. Sublingual estradiol was added to the 2022 WPATH guidelines; one small pharmacokinetic study suggested there can be a peak estradiol level after the first hour of administration and that twice-a-day dosing may be needed for testosterone suppression.

Antiandrogens can be used in conjunction with estrogen for testosterone suppression. In the United States, spironolactone is the most widely available antiandrogen. Cyproterone acetate is not available in the United States. Gonadotrophin-releasing hormone (GnRH) agonists are also utilized at times to block the production of testosterone; these are given as an injection and can be costly. 5-alpha reductase inhibitors are mentioned in some guidelines as being helpful in treating scalp hair loss and skin changes, although action (blocking the conversion of testosterone to the more active 5-alpha-dihydrotestosterone) may be limited in people who already have significant androgen blockade. Bicalutamide is also not currently recommended in the guidelines as it has not been adequately studied in feminizing GAHT, and testosterone levels cannot be followed for suppression. References for the Endocrine Society, WPATH, and University of California San Francisco (UCSF) guidelines are provided at the end of this chapter.

8. When can physical changes be expected to occur with feminizing GAHT?

Patients should be counseled that physical changes occur slowly, just as in puberty, although the feminizing effects and timing are widely variable from person to person. There are no data to suggest that larger doses or certain routes of administration lead to more rapid or "complete" changes; in fact, there can be increased adverse events with larger doses or higher estradiol levels. Typical changes seen over the course of the first year are fewer erections, skin changes, and fat redistribution. Changes in libido are an expected outcome and should be discussed with patients in advance in case this is something they would like to try to preserve. Breast growth and development, smaller/softer testes, decreased sperm production, and infertility may be permanent changes even if feminizing GAHT is stopped in the future. It is important to educate patients that maximum changes can take more than 3 years to achieve and may be less evident in adults who start GAHT at an older age. For TGD people who went through male puberty, voice pitch does not go higher with estrogen, and voice training with a speech-language pathologist is most effective.

9. What changes in laboratory values can be seen with feminizing GAHT, and how should they be monitored?

Estradiol levels are expected to increase when using feminizing GAHT. However, estradiol levels will not reflect the use of conjugated estrogens or ethinyl estradiol; these preparations are no longer recommended for routine use in GAHT. It is also expected that testosterone levels will decline on all types of estrogen therapy but may not be suppressed completely, hence antiandrogen medications are often needed. The Endocrine Society and WPATH guidelines suggest that serum estradiol levels not exceed 100–200 pg/mL and that testosterone levels be suppressed to <50 ng/dL. They also suggest that patients be evaluated every 3 months for the first year with measurements of serum estradiol and testosterone, with the addition of electrolytes if on spironolactone. Thereafter, assessments and laboratory testing can be done once or twice a year, if the values are stable. Serum triglycerides may increase on oral estrogen therapy but this can be mitigated with the use of transdermal preparations. Estrogens also typically increase high-density lipoprotein cholesterol levels. Prolactin elevations have been reported as well, with or without symptoms of hyperprolactinemia, and most typically with cyproterone acetate, though routine monitoring is no longer recommended.

10. What are the contraindications to initiating feminizing GAHT?

Although there are no absolute contraindications to initiating estrogen in TGD people, the risk for some conditions may increase with feminizing GAHT. The highest risks are that of venous thromboembolism (VTE) and infertility. Other conditions with likely increased risk in the presence of additional risk factors include cardiovascular or cerebrovascular disease, meningioma (cyproterone), polyuria/dehydration (spironolactone), and cholelithiasis. Possible increased risk has been seen for hypertension, erectile dysfunction, and diabetes. The risks and benefits of feminizing GAHT should be discussed with each patient. At times, we have found consultation with colleagues in other specialties, such as cardiology, neurology, or hematology, to be useful regarding risk factors and management of cardiovascular and thromboembolic disease in higher-risk patients.

11. Is there a role for progesterone in feminizing GAHT?

There are no data to support the routine use of progesterone for breast growth in TGD patients taking feminizing GAHT. One study that evaluated different hormone protocols (with and without progesterone) did not find a difference in rates of requests for breast augmentation among the various protocols. In Turner syndrome patients, there are concerns that early addition of progesterone to estrogen therapy can cause less breast growth overall. In addition, concerns have been raised regarding the role of progesterone in the development of breast cancer and VTE in cisgender women. In the Women's Health Initiative (WHI), conjugated equine estrogens plus medroxyprogesterone given to older cisgender women was associated with the increased risk of breast cancer and VTE compared with that in the estrogen-only arm of the study. Medroxyprogesterone may also have unfavorable effects on lipid profiles, weight, and mood. Some providers consider bioidentical micronized progesterone only after some time (e.g., 1–2 years) on estradiol in patients who wish to try it but, again, there are no data to support the routine use of progesterone in people taking feminizing GAHT. We have also seen the use of depot medroxyprogesterone for testosterone suppression though data are also lacking for its routine use.

12. Is the risk of blood clots increased for people taking feminizing GAHT?

Some studies have also suggested an increased risk for VTE in people taking feminizing GAHT. These include a review of mostly European TGD cohorts showing that transgender women were at increased risk of VTE but mostly with the use of ethinyl estradiol, which is no longer recommended due to the increased risk of VTE with its use. Another recent metaanalysis of mostly uncontrolled and observational studies (including similar cohorts as above) concluded that data regarding the risk of VTE, myocardial infarction, stroke, and mortality were insufficient to draw conclusions (i.e., too few events reported); however, events were reported more often in transgender women than in transgender men. In the United States, the Study of Transition, Outcomes, and Gender (STRONG) cohort, consisting of 6456 Kaiser Permanente members, reported a higher incidence of VTE among the transfeminine cohort compared with reference females and males. The transfeminine cohort in the study had a higher incidence of VTE, with 2- and 8-year risk differences of 4.1 (95% CI: 1.6–6.7) and 16.7 (95% CI: 6.4–27.5) per 1000 persons relative to reference men, and 3.4 (95% CI: 1.1–5.6) and 13.7 (95% CI: 4.1–22.7) relative to reference women, though absolute VTE rates remained very low.

13. How does feminizing GAHT affect mortality?

The largest mortality study, to date, from the Amsterdam Cohort of Gender Dysphoria had a median follow-up of 11 years in almost 3000 transgender women. Their median age was 30 years at GAHT initiation and 25% were >42 years of age at GAHT start. There was a significant increase in the standardized mortality ratio compared with the general population of both men and women, analyzed separately. The increased mortality risk was mainly attributable to HIV, suicide, lung cancer, and cardiovascular disease. In a subgroup analysis of people who ever used ethinyl estradiol, a similar mortality risk was seen. This is also a reminder that, although gender dysphoria can be alleviated with GAHT, it is important to provide appropriate assessment and treatment for depression and other suicide risk factors. Transgender women also have higher rates of HIV infection compared with the general population, with even higher rates among sex workers. HIV screening for high-risk patients and referral to a preexposure prophylaxis (PrEP) clinic should be considered, when appropriate.

14. What are the options for masculinizing GAHT?

For most patients with gender incongruence or gender dysphoria pursuing masculinizing GAHT, testosterone is the mainstay of therapy. It is typically given via subcutaneous or intramuscular injection with weekly or every-other-week dosing of testosterone enanthate or cypionate. Testosterone undecanoate every 3 months is also available in some areas but requires some additional paperwork and must be given in a health care facility due to concerns for pulmonary oil microembolism. Testosterone can also be administered via transdermal gel, depending on patient preference, compliance, insurance coverage, and cost. The testosterone patch is no longer available in the United States as of 2023. The new oral testosterone may increase blood pressure and has been studied in fixed doses, but its use in masculinizing GAHT regimens deserves further research. GnRH agonists or progestins have been used when menses persist beyond the first 6–12 months of GAHT. References for the Endocrine Society, WPATH, and UCSF guidelines are provided at the end of the chapter.

15. What are the contraindications to initiating masculinizing GAHT?

Although there are no absolute contraindications to initiating testosterone in TGD people, the conditions with the highest risk per the guidelines are polycythemia with a hematocrit >50%

and infertility. Other conditions, listed as likely increased risk, include acne, androgenic alopecia, hypertension, sleep apnea, weight gain, decreased HDL, and increased LDL cholesterol. In the presence of additional risk factors, testosterone therapy may increase the risk of cardiovascular disease and hypertriglyceridemia.

16. When can physical changes be expected to occur with masculinizing GAHT?

As noted above, patients should be counseled that physical changes occur slowly, just as in puberty, although person-to-person masculinizing effects are widely variable. There are no data to suggest that larger testosterone doses or certain routes of administration cause more rapid changes, and in fact, there can be increased adverse events with larger doses and supraphysiologic testosterone levels. The typical changes begin within 1–6 months and include skin oiliness/acne, cessation of bleeding, and body fat redistribution with increased muscle mass, but maximal changes can take up to 5 years or more. Clitoral enlargement and deeper voice can also start within 1–6 months but may be permanent if testosterone is discontinued in the future. Scalp hair loss and facial/body hair growth can have an onset between 6–12 months and may also be permanent even if testosterone is discontinued in the future.

17. What changes in laboratory values can be seen with masculinizing GAHT, and how should they be monitored?

As serum testosterone levels rise, estradiol and gonadotropin levels will become suppressed. The guidelines suggest aiming for a testosterone level midway between injections of 400–700 ng/mL or having testosterone levels within the laboratory's male reference range. The guidelines advise monitoring levels every 3 months for the first year and then once or twice yearly going forward. It is no longer recommended to routinely monitor estradiol levels in patients on masculinizing GAHT.

Hematocrit will frequently increase on testosterone therapy and may necessitate a dose reduction or the use of a different testosterone formulation/route of administration. Other etiologies of an elevated hematocrit, such as obstructive sleep apnea, tobacco use, and recent move to higher altitude, should be investigated in addition to family history. Changes in the lipid profile with increases in serum triglycerides and LDL cholesterol with concomitant decreases in HDL cholesterol have been observed. The Endocrine Society guidelines suggest checking hemoglobin or hematocrit at baseline, every 3 months for the first year of testosterone therapy, and then once or twice yearly. They also suggest measuring weight, blood pressure, and lipids at "regular" intervals.

18. How does masculinizing GAHT affect mortality?

The largest mortality study from the Amsterdam Cohort of Gender Diversity had a median follow-up of 5 years in 1641 transgender men. The standardized mortality ratio was significantly increased compared with the general population of women but not the general population of men. It should be noted that the median age at GAHT start was 23 years, with 25% of the trans men aged >32 years at GAHT initiation. The higher mortality compared to the general population of women was driven by nonnatural causes and there was no increased mortality risk from cardiovascular disease, cancer, or infections.

19. How might GAHT management be different for nonbinary patients?

The available guidelines are rather binary in recommendations for GAHT regimens and hormone levels. Some nonbinary patients may feel comfortable with binary hormone levels and physical changes. Some nonbinary patients may feel best when they are taking lower hormone doses and/or have hormone levels between male and female reference ranges. However, we do not yet have predictors for which masculinizing or feminizing physical effects nonbinary patients may experience, especially if taking lower doses of GAHT. As with all patients, management decisions should be individualized and shared between prescriber and patient, with discussions about the risk benefits, and alternatives to specific doses and hormone levels. The UCSF guidelines have recommendations for initial GAHT doses ("low" dose) that may be advisable for some nonbinary patients depending on their goals. The 2022 WPATH guidelines added a chapter on nonbinary people that further describes management considerations.

20. What considerations are there for older adults who wish to start or continue GAHT?

As the general population ages, so do TGD patients. Questions arise over the safety of GAHT in the older transgender population, where aging-related comorbidities are present. There have been no randomized controlled trials investigating the safety of starting or continuing various hormone formulations or routes of administration in older transgender patients, especially regarding cardiovascular disease and mortality. Experts have suggested that initiation of GAHT in older TGD people has no disproportionate risks and that older age itself should not be a contraindication to initiating or continuing GAHT. Other areas in need of investigation include dose reductions or GAHT discontinuation after a certain age (although the risk of bone density loss may outweigh any unforeseen benefits, especially in the setting of gonadectomy, if part of the surgical history).

The 2022 WPATH guidelines added the recommendation to use transdermal estrogen in transgender women aged ≥45 years to mitigate VTE risk. There is currently no similar recommendation for transdermal testosterone in older transgender men. A discussion of the risks and benefits, past medical and family histories, current comorbidities, and any modifiable behaviors that may increase risks while on GAHT should be conducted with older TGD patients as with younger individuals. Additional topics that have been suggested for future studies among the aging TGD population include palliative care and end-of-life issues.

21. When is gender-affirming surgery indicated?

There are many types of gender-affirming surgery, and surgical transition should not be required of TGD patients. Depending on laws for a given area, surgical transition may still be required for patients to change their legal name, gender marker, or birth certificate. Many transmasculine patients will seek a bilateral mastectomy or "top surgery," which does not require a specific duration of testosterone therapy prior to surgery. Breast implants and orchiectomy are often requested by transfeminine patients. Some TGD patients will also seek facial feminization or masculinization surgery. Gender-affirming genital surgery or "bottom surgery" can be done with the creation of a neo-vagina or phalloplasty. Metoidioplasty, wherein the clitoris is brought forward to assist with urinating from a standing position, is also an option for transmasculine patients. The 2022 WPATH guidelines recommend at least 6 months of GAHT prior to gender-affirming surgery unless medically contraindicated or hormone therapy is not desired by the patient. One reason to postpone breast augmentation surgery is to maximize breast growth by feminizing GAHT to optimize surgical (aesthetic) results. In the United States, although more insurance companies are covering gender-affirming surgeries, persistent barriers include access to a trained surgeon, lack of insurance, and cost. After gonadectomy, GAHT doses can generally be decreased to reflect physiologic dosing because there is no further need for hormonal suppression of the endogenous hormones, and spironolactone can be discontinued after orchiectomy.

22. How common is gonadectomy in transgender and gender-diverse patients, and why is that important?

We do not yet fully understand if there are differences in health outcomes (and implications for dosing changes) among TGD patients on GAHT who have or have not had gonadectomy. Most published longitudinal data (e.g., cardiovascular disease risk, body composition, bone density, mental health, quality of life, etc.) have come from the European Network for the Investigation of Gender Incongruence (ENIGI) and the Amsterdam Cohort of Gender Dysphoria. Additionally, most systematic reviews and metaanalyses have analyzed data that come from these cohorts. Because of the differences in access to surgery, the ENIGI patient population has had much higher rates of gender-affirming surgery (in particular, gonadectomy); a Dutch cohort with 86.7% transgender women and 94% transgender men having had gonadectomy and a Belgian cohort with 64.8% transgender women and 85.5% transgender men having had gonadectomy.

In contrast, the 2015 United States Transgender Survey reported that only 25% of respondents had undergone *some form* of transition-related surgery, with only 14% of transgender men having had a hysterectomy—with the status of the ovaries not specified—and only 11% of transgender women have had an orchiectomy. In that survey, 55% of those who sought coverage for transition-related surgery in the past were denied. Lower rates of hysterectomy with or without oophorectomy (11%) in transmasculine adults and a much lower rate of orchiectomy (1.5%) in transfeminine adults were seen in the STRONG cohort from Kaiser Permanente.

23. How should transgender and gender-diverse patients be counseled about fertility preservation?

In accordance with guidelines, TGD patients should be advised about fertility preservation options prior to initiation of GAHT due to decreased fertility/sexual function after starting and while taking GAHT. Sperm and oocyte cryopreservation are available but can be expensive and typically not covered by insurance. The risks of permanent infertility with long-term GAHT are not known currently. If fertility is desired after the initiation of GAHT, typically, hormones are discontinued for some period, with the aim of allowing endogenous gonadal function to resume. There have been cases of transmasculine adults getting pregnant while taking and after stopping testosterone with good outcomes.

It is also important to counsel TGD patients that while GAHT may lead to infertility, it is not a reliable contraceptive. Providers should take a thorough sexual history and counsel patients regarding contraception, as appropriate.

24. What are the recommendations for osteoporosis screening in transgender and gender-diverse adults?

Generally, if patients continue GAHT, sex steroids assist in the maintenance of bone density. Testosterone is converted to estradiol, which is considered a key component of bone in cisgender men. However, if TGD patients stop GAHT after gonadectomy, bone loss can be considerable. There are some concerning data to suggest that a large proportion of transgender women have low bone mineral density prior to starting estrogen, which may be multifactorial and include social and behavioral disparities compared to their peers. Fracture data are limited to the Amsterdam Cohort of Gender Dysphoria which concluded that fracture risk was higher in older transgender women (aged ≥50 years) compared to age-matched reference men, fracture risk in younger transgender women (aged <50 years) tended to be increased compared to age-matched reference women, and transgender men did not have higher fracture risk compared to the general population. The 2017 Endocrine Society guidelines recommend that a baseline bone density be considered in all transgender women, with screening of low-risk patients to begin at age 60 years or if GAHT use stops. For transgender men, they suggest screening if testosterone use stops or other risks arise.

In 2019, the International Society for Clinical Densitometry added recommendations for DXA scans in TGD adults with indications including history of gonadectomy or therapy that lowered endogenous gonadal steroid levels prior to GAHT and hypogonadism with no plan to take GAHT. They also recommended that while T-scores should be calculated using a uniform Caucasian female normative database for all transgender individuals of all ethnic groups, as they are for cisgender individuals, Z-scores use the normative database that matches the individual's gender identity, and bone density of nonbinary individuals be compared against the normative database that matches their sex recorded at birth.

25. What are the recommendations for cancer screening in transgender and gender-diverse adults?

Screening for cancers should be done on the basis of existing tissues for which there are cancer screening guidelines. For example, both transgender women and transgender men may have breast tissue. A trans man with breast tissue should be screened with mammography or other imaging modality, as deemed appropriate by age, family history, and gender-affirming chest surgery history. The UCSF Gender Affirming Health Program suggests yearly or every-other-year mammography once a transgender woman is older than 50 years of age and has been on estrogen therapy for >5–10 years. The 2017 Endocrine Society guidelines suggest breast cancer screening for transgender women be the same as for cisgender women per national guidelines.

Cervical cancer screening with Papanicolaou (Pap) testing in transgender men with cervical tissue should follow age-related guidelines for cisgender women. Because this can be an uncomfortable procedure and there are reports of a higher incidence of unsatisfactory results in transgender men on testosterone therapy, it is particularly important that this testing be done by an experienced provider and/or considerations be made for self-swab performed by the patient. In addition, it is our personal experience that performing Pap testing in a gender-neutral space can improve compliance rates and ease patient distress.

There have been case reports of prostate cancer in transgender women. Prostate cancer screening should also be done as appropriate for age and other risk factors while taking into consideration the risks and benefits of screening. With testosterone, suppression while taking feminizing GAHT, the threshold for prostate-specific antigen may need to be lowered if being used for screening or monitoring.

All other vaccinations and preventive cancer screening should be performed in TGD adults as appropriate for age and family history.

26. How do I counsel transgender and gender-diverse patients regarding smoking cessation?

Recent studies have shown smoking to be a major risk factor for VTE in people on hormone therapy, regardless of gender identity. A 2017 retrospective study of 156 transgender patients found that patients (64% of transgender women and 25% of transgender men) were more likely to quit smoking after tobacco cessation counseling compared with the general population of adult smokers offered tobacco cessation counseling (6% in a given year). Some guidelines suggest a strong preference to use transdermal estrogen in patients who smoke, although current smoking status is not an absolute contraindication to starting GAHT. The same counseling strategies for smoking cessation should be applied to patients regardless of gender identity. There is a need for more studies on the health impacts of marijuana smoking and vaping in TGD populations taking GAHT.

27. How can providers assist transgender and gender-diverse patients with legal name and gender marker changes?

There will be variations across states and countries as to the requirements for legal document changes. The Local Department of Motor Vehicle (DMV) and the federal websites for passports and birth certificates can provide up-to-date information. Depending on locations, a letter from a physician may still be required stating that the patient is receiving medical care and that the gender transition is "complete." A website that provides US state- and territory-specific information about how to update name and gender markers on state and federal identification documents and records is available from the National Center for Transgender Equality (https://transequality.org/documents).

KEY POINTS

- Gender incongruence can lead to gender dysphoria, which is the distress and unease that may occur when a person's gender identity and/or gender expression differs from the sex recorded at birth.
- Gender-affirming hormone therapy is associated with many benefits. Hormone preparations that allow for monitoring of serum hormone levels (estradiol, testosterone) are preferred, with dose adjustments made to keep estradiol (in transfeminine adults) and testosterone levels (in transfeminine and transmasculine adults) within guideline-recommended ranges and to balance risks, benefits, and expectations.
- There appears to be an increased risk of thromboembolic events in transgender women taking GAHT and concerns about possible increased risks for cardiovascular disease and mortality, which demonstrate the need for additional high-quality, prospective research.
- The long-term effects of GAHT, especially among the growing older and gender-diverse populations in the United States and around the world, deserve further research.
- Endocrinologists should be familiar with GAHT guidelines and utilize a multidisciplinary approach with primary care and other specialists to provide comprehensive care. Informed discussion with patients is a key part of making treatment decisions.

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Use and Abuse of Anabolic–Androgenic Steroids and Androgen Precursors

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CHAPTER 58

1. What are anabolic–androgenic steroids?

Anabolic–androgenic steroids (AASs) are a group of steroid hormones derived from the chemical modification of testosterone. The precursor to testosterone is cholesterol; endogenous synthesis is limited by cholesterol delivery to mitochondria for modification. After synthesis and secretion, testosterone is further converted to strong androgens to include dihydrotestosterone (DHT) via 5-alpha-reductase, and weak androgens to include dehydroepiandrosterone (DHEA) and androstenedione. Testosterone is also converted via aromatase to estradiol, an active metabolite, although not an AAS. The terms *anabolic* and *androgenic* derive from their ability to promote positive nitrogen balance and accretion of lean body mass as well as masculinization.

2. Where are AASs made?

In males, testosterone is made in the Leydig cells of the testes. In females, testosterone is made by the theca cells of the ovary. Testosterone is then peripherally converted to DHT in the skin, prostate, and external genitalia. DHEA, one of the most important weak androgens, is primarily made by the adrenal cortex.

3. Summarize the biological effects of AASs.

Endogenous AASs have diverse effects with three distinct physiologic surges. The first occurs during the fetal period at weeks 6 through 8 of gestation, when they promote the development of male genitalia. The second surge occurs during the neonatal period, when they are involved in the growth of the phallus to normal size, in testicular descent, and in spermatogonia development. The final surge assists in the development of secondary sexual characteristics during puberty, including the growth and development of the prostate, seminal vesicles, penis, and scrotum. Pubertal changes in hair growth and sebaceous glands result in the male pattern of hair growth on the chin, pubic area, chest, and axillary regions, as well as acne provocation via increased sebum production. Vocal cords begin to thicken, along with enlargement of the larynx, resulting in voice deepening.

Data indicating decreased urinary nitrogen levels support AAS effects on protein anabolism, resulting in an increase in lean body mass, specifically in the upper girdle, and alterations of fat distribution. Further structural changes occur with increases in bone mineral density and long bone growth, and with the closure of the epiphyses. Neurologic changes include increased libido and spontaneous erections. Other effects include the promotion of wound healing; stimulation of liver release of clotting factors and erythropoietin with a secondary increase in hematocrit; and suppression of high-density lipoprotein (HDL) synthesis (Table 58.1).

4. How does testosterone mediate its effects via estradiol?

During puberty, when testosterone levels surge to stimulate bone growth, peripheral androgen conversion via aromatase also peaks. Newly synthesized estradiol promotes epiphyseal closure during puberty, counteracting the effects of testosterone. In patients with aromatase deficiency or estradiol receptor dysfunction, long bones continue to grow, but osteoporosis develops because estradiol is the most important regulator of bone mass accretion. Of note, this mechanism is different from estrogen's effect on osteoclasts and osteoblasts associated with osteoporosis in postmenopausal women.

5. What is the correlation between AAS and age, and how is this important?

Total, free, and bioavailable testosterone levels decrease with age. This contributes to the decrease in muscle mass, increase in fat, decreased libido, increased fatigue, and minor decreases in cognitive function seen in the elderly.

TABLE 58.1 Physiologic Effects of Androgens

Fetal Period

- Internal and external male genitalia development

Neonatal Period

- Phallus size development
- Testicular descent
- Spermatogonia development

Puberty

- Growth and development of prostate and seminal vesicles
- Increased size and width of the penis
- Increased scrotal size
- Increased male pattern hair growth
- Increased skin thickness
- Increased sebaceous gland production, resulting in oily skin and development of acne
- Deepening of voice via vocal cord thickening and enlargement of larynx
- Increase in lean body mass
- Altered fat distribution
- Increased bone mineral density
- Long bone growth and closure of epiphyses
- Increased libido, sexual desire, and spontaneous erections
- Fibroblast stimulation promoting wound healing
- Liver synthesis of clotting factors and erythropoiesis
- Suppression of high-density lipoprotein cholesterol formation

Adult

- Maintenance of testosterone tissue effects

6. How do AASs exert their effects?

Approximately 50% of circulating testosterone is strongly bound to sex hormone–binding globulin (SHBG); 40% is weakly bound to albumin; and 2% is unbound or free. The albumin-bound and unbound forms constitute the "bioavailable" and, thus, active forms of testosterone. AASs act by binding to specific intracellular androgen receptors located throughout the body; this interaction mediates the androgenic and anabolic effects of androgens. Dihydrotestosterone, being a strong androgen, has a very high affinity for androgen receptors. Estradiol, formed by aromatase conversion of testosterone, exerts its effects by binding to estrogen receptors throughout the body.

7. How are androgens metabolized, and why is it necessary to modify testosterone for administration?

AASs are rapidly metabolized by the first-pass effect through the gut and the liver, making oral testosterone supplements highly ineffective in the absence of modification. Alkylation of testosterone confers resistance to hepatic metabolism and results in AASs that can be administered orally. Esterification of testosterone emulsifies testosterone for intramuscular injection. The addition of carbon chains to the ring structure of testosterone increases fat solubility and extends the duration of action.

8. What are the signs and symptoms of low or high androgen levels?

Patients with low androgen levels may complain of fatigue, hypoactive sexual desire, erectile dysfunction, diminished pubic and/or facial hair, and testicular atrophy. Other findings include diminished prostate size, abnormal sperm morphology, absent motility of sperm, and hypoproliferative normochromic anemia. Patients with elevated levels may complain of resistant acne or sudden-onset acne. Women especially will develop hirsutism and irregular menses.

9. What are the indications for AAS therapy?

AASs are indicated for use in male hypogonadism and constitutional delay of growth and puberty. Use for stimulation of growth is cautioned because it may concomitantly accelerate epiphyseal closure and thereby limit ultimate height achievement. Androgens are also used as prophylaxis in hereditary angioneurotic edema and as second-line therapies for osteoporosis and aplastic or hypoplastic anemias. Gynecologic uses include treatment of endometriosis with weak androgens; reduction of postpartum breast engorgement in conjunction with estrogen; and elimination of estrogen-mediated menstrual bleeding for postmenopausal women undergoing hormone replacement. In oncology, androgens can be used to suppress some breast tumors in premenopausal women.

10. Are there any other potential uses for AASs?

AASs may help elderly men by increasing body weight and muscle mass, preventing bone loss (vertebral but not femoral bone density), and improving hematocrit; however, AASs are not without side effects. There is also ongoing research on using androgens as male contraceptives, in chronic obstructive pulmonary disease, and in other hypogonadal wasting syndromes, such as muscle wasting in human immunodeficiency virus (HIV) infection and glucocorticoid-induced muscle and bone wasting. All of these uses are still under investigation.

11. What are the uses for androgen antagonists and/or inhibitors?

5-alpha-reductase inhibitors are used to diminish testosterone conversion to DHT in peripheral tissues, most importantly in the prostate gland and in hair follicles. They have US Food and Drug Administration (FDA) approval for the treatment of benign prostatic hyperplasia and to combat early male-pattern baldness. Androgen receptor antagonists are also used to treat metastatic prostate cancer and female hirsutism.

12. How common is abuse of AASs?

First noted in the 1950s, AAS abuse was mostly limited to bodybuilders, other muscle-building enthusiasts, and various professional athletes. It is now known that AAS abuse is far more widespread. According to the results of one study, 3.3% of high school students reported anabolic steroid use; in another study, the use of products to improve appearance, muscle mass, or strength was reported by both girls and boys at rates of 8% and 12%, respectively. The National Institute of Drug Abuse (NIDA) report in 2007 noted use in 2.3% of boys versus 0.6% of girls. The NIDA recently estimated that over half a million grade 8 through grade 10 students are abusing AASs. Another study found that 1,084,000 Americans, or 0.5% of the adult population, have admitted to using AAS.

13. Who is at risk for using illegal AASs?

In the world of competitive athletics, bodybuilders are the biggest offenders with regard to AAS abuse. Because AASs increase hematocrit through enhanced erythropoietin production, they may also be used by athletes participating in endurance-oriented sports. Nonathletes may use AASs solely to improve their appearance. Surveys have shown that the percentage of students who reported lifetime AAS use has increased from 2.7% to 6.1% in the past decade. Most users are men, although up to 2% may be women. Other risk factors include involvement in school sports and the use of other illicit drugs, alcohol, or tobacco.

14. Do AASs truly help athletes?

Both athletes and coaches are likely to answer with an unequivocal yes. AASs used in conjunction with adequate protein, carbohydrate intake, and proper training in experienced athletes seem to induce greater and more rapid gains. A study comparing supraphysiologic doses of testosterone enanthate with placebo in eugonadal men found clear increases in muscle size and strength, with or without weight-training exercise. Studies of AAS in athletes have shown an increase in body weight and lean body mass but no significant decrease in the percentage of body fat. Not only do muscle fibers gain in cross-sectional diameter with anabolic steroid use, but new muscle fibers are also formed. The upper regions of the body show the most prominent gains in muscle mass as a result of AAS use because of the relatively larger number of androgen receptors in these areas.

15. What doses of AASs are used in attempts to enhance sports performance and appearance?

Doses used for illicit purposes are markedly higher (≥10-fold) than physiologic and therapeutic doses. Furthermore, multiple agents are often used in so-called stacking regimens or arrays, in which multiple steroids at increasing doses are used to derive further effects. The drugs are often taken in 6–12-week cycles, with variable periods off the drugs, but some athletes may use them for as long as ≥1 year. Human chorionic gonadotropin may be used at the end of a cycle to prevent inhibition of gonadal function. Little is known about precise doses or stacking regimens; however, some anecdotal information is available.

16. What are the potential adverse effects of AAS use?

The most common side effects are hepatic dysfunction including cholestatic jaundice and the development of hepatic neoplasms; the most worrisome is peliosis hepatis, which can rupture causing death. Other common side effects include gynecomastia, acne, male-pattern baldness, increased aggression, and alterations in the cholesterol profile including an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) cholesterol. Fortunately, most side effects are temporary and reversible with cessation of AAS (Table 58.2). Long-term use is associated with a reduction in the production of natural sex hormones; this, however, is usually reversible but may take over a year to resolve. There is also an increase in cardiovascular disease as a result of fluid retention, exacerbation of hypertension and dyslipidemia, increased liver synthesis of clotting factors, development of polycythemia, and vasospasm induction via effects on vascular nitric oxide. Males may be at increased risk for the development of prostate problems in previously benign or local disease, impotence, and testicular atrophy resulting in infertility. Women may experience menstrual irregularities, such as oligomenorrhea or amenorrhea, and virilizing effects such as hirsutism, clitoromegaly, and deepening of the voice. In adolescents, there is a risk of premature epiphyseal closure leading to a reduction in final adult height and psychological dysfunction caused by androgen effects on brain development.

TABLE 58.2 Potential Adverse Effects of AAS Use and Abuse

SYSTEM/ORGAN	ADVERSE EFFECTS
Liver	• Cholestatic hepatitis • Peliosis hepatis (hemorrhagic liver cysts) • Liver tumors—benign and malignant (oral agents)
Cardiovascular	• Stroke and myocardial infarction incidence increased • High-density lipoprotein (HDL)—cholesterol reduced and low-density lipoprotein (LDL)—cholesterol increased • Left ventricular enlargement (cardiac androgen receptors) • Increased vasomotor tone and vasospasm (effects on vascular nitric oxide)
Reproductive	• Testicular atrophy • Oligospermia/azoospermia • Priapism • Gynecomastia/breast tenderness • Natural sex hormone production diminished • Prostate disease worsening (benign/local disease) • Clitoral hypertrophy • Menstrual irregularity, amenorrhea, and infertility
Hematologic	• Platelet count and aggregation increased • Polycythemia
Psychological	• Aggressive behavior • Psychotic symptoms • Dependence/Withdrawal • Depression
Skin	• Sebum production and acne increased • Male-pattern baldness • Hirsutism (women)
Other	• Fluid retention resulting in peripheral edema and exacerbation of hypertension and/or congestive heart failure • Deepening of voice • Stunted growth (for adolescents) • Epiphyseal closure with decreased final adult height

AAS, Anabolic–Androgenic Steroid

17. What are the neuropsychiatric implications of AAS use?

Major mood disorders and aggressive or even criminal behavior have been previously reported in the literature. One study performed in 1994 compared neuropsychiatric behavior in men actively taking AASs and those not taking AASs. One hundred and sixty men recruited from gyms responded to a questionnaire about androgen use and psychiatric symptoms. Psychiatric symptoms, including major mood disorders and aggressive behavior, were more common in men who had taken androgens than in those who had never taken androgens; among the former, the symptoms were more common while they were taking androgens. Several studies have also described an association between nonmedical use of androgens and risky or even criminal behavior. In mail surveys of approximately 10,000–15,000 college students from 1993 to 2001, nonmedical use of androgens was associated with cigarette smoking, other illicit drug use, drinking and driving, and alcohol use disorder.

18. What screening tests are used to detect AAS use in athletes?

Urine samples can be evaluated via mass spectroscopy and gas chromatography, where direct confirmation comes from the measurement of protein kinase C (PKC). PKC reflects an exogenous synthetic origin, ruling in or out a potential physiologic anomaly. The World AntiDoping Agency (WADA) is currently using two main methods for the detection of AAS use. An increased ratio of urine testosterone to epitestosterone (T/E ratio >4:1) is confirmatory of AAS use. The biggest pitfall of this diagnostic study is that positive results can be masked by taking epitestosterone or gonadotropins. The second is the ratio of carbon 13 (C13)–carbon 12 (C12). This test is performed by using isotope mass spectrometry to measure the urinary ratio of testosterone metabolites (C13 and C12). This is currently used as a confirmatory test for people who test positive on testosterone/epitestosterone (T/E) ratio assessment. Exogenous testosterone is manufactured from plant sterols, which have a lower C13/C12 ratio, compared with their animal counterparts. The biggest advantage of C13/C12 over the T/E ratio is that the results are not masked by the use of epitestosterone or gonadotropins. Furthermore, urine samples with a high ratio of testosterone to luteinizing hormone (LH) >30 suggest AAS abuse because LH secretion is suppressed in subjects using testosterone. Detection of derivatives of testosterone can be done via gas chromatography and mass spectrometry as long as the athlete is actively taking AASs at the time of the test. Derivatives of testosterone will also lead to an increase in the T/E ratio.

19. What are some methods currently being used by professional athletes and recreational users to avoid detection of AAS?

Several methods to avoid detection have been described in the literature and in anecdotal sources. The most common is to discontinue the medication prior to laboratory testing. Urine dilution by drastically increasing fluid intake and using diuretics prior to testing are other frequently used methods. Isolated cases in which substances have been directly placed in the urethra to confound test results have also been reported. Other methods include simply refusing to provide urine or blood samples, and more recently, the use of designer steroids has been reported. In 2003, the Olympic Analytical Laboratory at the University of California, Los Angeles (UCLA) discovered the first designer steroid, tetrahydrogestrinone (THG), which was manufactured by a private laboratory. This drug could not be detected using standard testing methods and was only confirmed by liquid chromatography with tandem mass spectrometry.

20. What are the so-called androgen precursors or prohormones?

These are products/supplements advertised to be metabolized to testosterone or other active metabolites. In 2004, Congress passed the *Anabolic Steroid Control Act*, banning prohormones indefinitely. Data from the past decade are mixed, showing that acute oral ingestion of ≥200 mg daily of androstenedione or androstenediol modestly increases serum testosterone and estrogen concentrations in men and women; however, doses <300 mg taken for up to 12 weeks have shown no effect on body composition or physical performance.

21. What are SARMs and are they really effective?

Selective androgen receptor modulators (SARMs) are nonsteroidal orally active molecules designed to bind to androgen receptors in specific tissues such as muscle and bone. In the last decade, they have become popular as performance-enhancing drugs. None is approved for human use, and no research is available to support their efficacy. Many of these SARMs are sold online, and the majority have inaccurate labeling. In a study of 44 SARM products purchased from the Internet and analyzed by procedures approved by the WADA, only 18 had accurate labeling (e.g., the label showed the correct SARM and dosage). Four products contained no active compounds, and the remainder were inaccurately labeled (most had at least one unapproved drug or substance [e.g., growth hormone secretagogues and/or androgens]).

22. Have androgen precursors been shown to be anabolic in men or women?

Yes. Recent literature has suggested that suprapharmacologic doses can be anabolic in certain situations; however, the situations and mechanism of action are unclear and side effects similar to AAS apply.

23. Is AAS becoming a global public health problem?

In 2013, the Centers for Disease Control and Prevention (CDC) reported an astonishing rate of use (3.2%) of AASs among high school students in the United States. The prevalence rate increased from 1991 to 2001 (2.7–5%) and then decreased between 2001 and 2013 (5–3.2%). The lifetime prevalence of use in high school girls and boys was 2.2% and 4%, respectively. Globally, a metaanalysis of 187 studies demonstrated that the overall global lifetime prevalence rate was 3.3% but was higher among men (6.4%) than among women (1.6%). The rate was higher among recreational athletes than among professional athletes (18.4% versus 13.3%) and varied by region (highest in the Middle East [22%] compared with other regions of the world [2–5%]).

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CHAPTER 59

Autoimmune Polyglandular Syndromes

Richard Millstein

1. What are autoimmune polyglandular syndromes?

Autoimmune polyglandular syndromes (APS) are a group of disorders characterized by the presence of at least 2 glandular autoimmune mediated diseases. There are two main forms of APS, type 1 and type 2. While they share a common name, these conditions differ in the immunologic processes that lead to endocrinopathies. Included in this group of disorders are APS 3 and IPEX or immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome.

Autoimmune Polyglandular Syndrome Type 1

2. What are the autoimmune endocrinopathies associated with APS 1?

This condition is characterized by chronic mucocutaneous candidiasis (70–80%), hypoparathyroidism (80–85%), primary adrenal insufficiency (60–70%), type 1 diabetes mellitus (<20%), hypogonadism (12%), thyroid disease (10%), and hypopituitarism (0–2%). Candidiasis tends to be the presenting condition, while the most common accompanying conditions are hypoparathyroidism and adrenal insufficiency.

3. Are there nonendocrine autoimmune disorders associated with APS 1?

Yes. Vitiligo, alopecia areata, autoimmune gastritis, pernicious anemia, autoimmune hepatitis, celiac disease, Sjogren's, rheumatoid arthritis, and myasthenia gravis can all be associated with APS 1.

4. At what age does APS 1 occur?

Components of APS 1 tend to appear in infancy or childhood around ages 3–5 years. They can also occur in early adolescence and usually will manifest within the first 20 years of life. APS 1 has also been called juvenile autoimmune polyglandular polyendocrinopathy or autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED). Incidence of APS 1 is <1:100,000.

5. Is there a genetic cause of APS 1?

Yes. APS 1 is caused by mutations of the AIRE (autoimmune regulator) gene. This gene helps distinguish cells that are self from nonself. It is a transcription regulator that promotes immunological central tolerance, thereby preventing the body from attacking itself. The AIRE gene is expressed in the thymus, lymph nodes, and peripheral blood cells.

6. What diagnostic approach should be taken?

Obtaining 21 hydroxylase antibodies will help determine if adrenal insufficiency is autoimmune in nature; however, the absence of these antibodies does not exclude autoimmune adrenal disease. If autoimmune adrenal insufficiency is the first to present, then screening should be done for type 1 diabetes and thyroid disorders. GAD 65 antibodies, islet cell antibodies, thyroid peroxidase antibodies, and thyroglobulin antibodies should be obtained.

Autoimmune Polyglandular Syndrome Type 2

7. What are the autoimmune endocrinopathies associated with APS 2?

APS 2 is characterized by thyroid disease (70–75%), type 1 diabetes mellitus (50–60%), primary adrenal insufficiency (40%), hypoparathyroidism (3%), and hypopituitarism (0–2%). Mucocutaneous candidiasis is not associated with APS 2.

8. Are there nonendocrine autoimmune disorders associated with APS 2?

Yes. These include vitiligo, autoimmune gastritis, alopecia areata, and pernicious anemia.

9. At what age does APS 2 occur?

APS 2 usually presents in the third to fourth decades of life. Childhood disease is extremely rare. The appearance of more than one autoimmune disease can take years to decades to manifest.

10. Are there genetic causes of APS 2?

Yes, APS 2 is a polygenic disorder associated with major histocompatibility loci. Most of the disease processes associated with APS 2 are associated with HLA alleles B8 and DR3.

11. What are Schmidt and Carpenter syndromes?

Schmidt's syndrome is a combination of primary adrenal insufficiency and Hashimoto's thyroiditis while Carpenter's syndrome is a combination of primary adrenal insufficiency and type 1 diabetes mellitus. These eponyms are currently out of favor for describing these conditions.

12. What is autoimmune polyglandular syndrome type 3?

Type 3 APS is defined by multiple autoimmune disorders primarily involving autoimmune thyroiditis and not including autoimmune adrenal disease.

13. What is IPEX syndrome?

IPEX syndrome is an immune regulatory disorder caused by a mutation of the FOXP3 gene. This disorder is characterized by early-onset type 1 diabetes mellitus, enteropathy, and dermatitis. Eosinophilia and elevated IgE levels are frequently present. First-line treatment for this disease is immunosuppressive therapy.

14. What thyroid diseases are associated with APS?

Autoimmune thyroiditis (Hashimoto's thyroiditis) and/or Graves disease are the autoimmune thyroid diseases that can be present in APS syndromes. Autoimmune thyroiditis results in hypothyroidism while Graves disease results in hyperthyroidism.

15. What hormone pathways are affected in the adrenal gland in primary adrenal insufficiency?

The glucocorticoid and mineralocorticoid pathways are both often affected in autoimmune adrenal disease.

16. How is APS diagnosed?

Screening can be accomplished based on current guidelines for the various components of APS. In young patients with type 1 diabetes or autoimmune adrenal failure, screening for other autoimmune diseases should be performed. In those with autoimmune adrenal disease, antibodies for type 1 diabetes mellitus and autoimmune hypothyroidism should be assessed every 2–3 years. If clinical disease is present then antibodies should be assessed. (See Table 59.1.)

Treatment of Autoimmune Polyglandular Syndromes

- Treatment is targeted to the organs/systems affected.

17. How do you treat mucocutaneous candidiasis?

The treatment of choice for mucocutaneous candidiasis is oral fluconazole 100–200 mg daily for 7–14 days. Response may be initially delayed if extensive skin/nail involvement is present. Fluconazole 100 mg three times weekly can then be used for suppressive therapy and itraconazole or posaconazole can be used in fluconazole refractive disease.

18. How do you replace thyroid hormone in hypothyroidism?

Hypothyroidism is treated with daily oral levothyroxine (brand or generic). The microgram (mcg) dose is based on weight and age.

1. Newborns: The dosage can be calculated roughly by multiplying kilogram (kg) weight by 10. (kg weight × 10 = mcg daily dosage).
2. Children: multiply kg weight × 4–6.
3. Adolescents: multiply kg weight by 2–4.
4. Adults: multiply kg weight by 1.6.

TABLE 59.1 Evaluation of Autoimmune Polyglandular Syndromes (APS)

AUTOIMMUNE DISEASE	ANTIBODY	LABORATORY
Type 1 diabetes	AntiGAD antibody, Islet cell antibody, zinc transporter 8 antibody	Elevated blood glucose and low c-peptide level
Hypothyroidism	TPO, Tg Ab	Elevated TSH and low thyroid hormones (T4 and/or T3)
Graves disease	TRAB, TSI	Suppressed TSH and elevated thyroid hormones (T4 and/or T3)
Primary adrenal insufficiency	21 hydroxylase antibody	Low cortisol and elevated ACTH. Consider an ACTH stimulation test.
Hypoparathyroidism		Low serum calcium and parathyroid hormone. 1,25 hydroxy vitamin D will also be low.
Hypogonadism	17α hydroxylase	Low estrogen/testosterone with elevated FSH/LH. (Post puberty age)

ACTH, adrenocorticotropic hormone; *FSH,* follicle stimulation hormone; *GAD*, glutamic acid decarboxylase; *LH,* luteinizing hormone; *Tg Ab*, antithyroglobulin antibody; *TPO*, thyroid peroxidase antibody; *TRAB*, TSH receptor antibody; *TSH,* thyroid stimulating hormone; *TSI,* thyroid stimulating immunoglobulin

5. If adrenal insufficiency is present then glucocorticoid treatment must be initiated prior to thyroid hormone replacement to ensure adrenal crisis is not precipitated.

19. How do you treat Graves disease?

Graves disease can be treated in one of three ways. Treatment choices include medication (methimazole or propylthiouracil), radioactive iodine, or surgery to remove the thyroid. If the thyroid becomes nonfunctional or is removed, thyroid hormone replacement must be initiated. If medication is used, the goal of treatment is a TSH in the normal range, determined by local laboratory ranges.

20. How do you replace insulin in type 1 diabetes mellitus?

Type 1 diabetes mellitus is treated with insulin. Initial insulin dosing is based on body weight and can range from 0.4 to 1.0 units/kg/day divided 50%/50% into basal/bolus therapy (long-acting/short-acting insulin) with higher doses being used during puberty. Insulin pump therapy can also be used to treat type 1 diabetes mellitus.

21. How do you treat hypoparathyroidism?

Hypoparathyroidism is treated with calcium and activated vitamin D (1,25 dihydroxy vitamin D or calcitriol); recently treatment with a long-acting injectable (once-daily) parathyroid hormone (PTH) analog, palopegteriparatide, has proven to be highly efficacious and safe. The goal of treatment is to keep the calcium in the low normal to just below normal range. A thiazide diuretic may help maintain serum calcium levels and prevent or reduce hypercalciuria.

22. How do you treat adrenal insufficiency?

Adrenal insufficiency is treated with glucocorticoid with or without mineralocorticoid replacement.

1. Children: Hydrocortisone 8 mg/m^2 body surface area divided into three or four daily doses. If aldosterone deficiency is present, fludrocortisone 100 mcg/day must be added to stabilize sodium levels; in infants, NaCl tablets are usually preferred.
2. Adults: Hydrocortisone 15–25 mg daily in two to three divided daily doses. Prednisone 5 mg daily can also be used if compliance is an issue. If aldosterone deficiency is present, fludrocortisone 50–100 mcg daily should be added without dietary salt restriction.
3. Doses of steroids must be doubled if acute illness occurs. It is also important to ensure the patient has an identification bracelet/necklace stating he/she has adrenal insufficiency should the patient be found unconscious.

23. How do you replace sex hormones?

Hypogonadism is treated with estrogen or testosterone depending on the sex of the patient. In pediatric patients care must be given to ensure proper bone development prior to initiating full hormone replacement. If 17α hydroxylase antibodies are positive, then ova/sperm preservation should be considered if reproduction potential is to be preserved.

KEY POINTS

Autoimmune Polyglandular Syndromes

- APS 1 consists of mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency as well as other autoimmune conditions.
- APS 2 consists of adrenal insufficiency, type 1 diabetes mellitus, and thyroid disorders as well as other autoimmune conditions.
- APS 1 and 2 can have nonendocrine components.
- The cause of APS type 1 involves the AIRE gene while APS type 2 is a polygenic HLA associated disorder.

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CHAPTER 60

Multiple Endocrine Neoplasia

Ethan Stortz, John J. Orrego, and Lauren Fishbein

1. What are the multiple endocrine neoplasia (MEN) syndromes?

Multiple endocrine neoplasia (MEN) refers to clinical syndromes involving neoplastic change, including hyperplasia and overt tumor formation, in two or more endocrine glands. These disorders are usually inherited in an autosomal dominant fashion but can occur de novo (more than 10%). These syndromes include MEN type 1 (MEN1), MEN type 2A (MEN2A), MEN type 2B (MEN2B), and MEN type 4 (MEN4).

2. Define the different MEN syndromes.

Table 60.1 defines the MEN syndromes and susceptibility genes.

3. Are there mnemonic devices to remember the different MEN syndromes?

MEN1 syndrome involves the three "Ps" of hyperparathyroidism, pituitary adenomas, and pancreatic neuroendocrine tumors.

Others have used the "decreasing P" and increasing "M" mnemonic to remember these major manifestations of MEN syndromes. MEN1 syndrome involves three "P's" as above, and the number of "Ps" for each MEN syndrome decreases with the number of "Ms" increasing from MEN1 to MEN2A (Medullary thyroid cancer, hyperparathyroidism, and pheochromocytoma) to MEN2B (medullary thyroid cancer, marfanoid habitus, mucosal neuromas, pheochromocytoma).

4. What causes MEN1?

The *MEN1* gene is found on chromosome 11 (11q13) and consists of 10 exons that encode a 610 amino acid protein known as Menin. Menin interacts with numerous proteins involved in genome stability, cell division and proliferation, and transcriptional regulation, including NFKB, SMAD3, CDK inhibitor, histone deacetylase, and histone methyltransferase. Most *MEN1* mutations are inactivating and consistent with a loss of tumor-suppressor gene function. The MEN1 phenotype is seen when a proband inherits one MEN1-affected allele from one parent and one normal allele from the other parent. When a somatic mutation inactivates the normal allele, tumor suppressor function is lost, and hyperplasia of the affected gland occurs. This is an example of Knudson's "two-hit" hypothesis. To date, over 1000 germline mutations have been discovered. These include frameshift, missense, nonsense, and splice-site mutations, as well as insertions and deletions. Complete exon deletions or even whole gene deletions have been observed and are harder to detect by traditional DNA sequence analysis, requiring separate deletion/duplication studies to be done. Furthermore, promoter or epigenetic changes will not be found in traditional DNA sequencing or deletion/duplication studies. So, a subset of patients may not have a mutation found but meet clinical diagnosis for MEN1.

5. What is a phenocopy?

Phenocopy, or "phenotypecopy," refers to a phenotype of disease manifestation without the expected characteristic mutation. Between 5% and 25% of patients who meet clinical criteria for MEN1 syndrome (see Question 6) have no identified pathogenic variant of the *MEN1* gene. Differences in methods for mutation identification (see Question 4) and phenotype assignment may be partly responsible for variability in detecting *MEN1* mutations, although some patients may have mutations involving genes other than *MEN1 (CDKN1B* for example*)*.

6. How is the diagnosis of MEN1 made?

The diagnosis of MEN1 is made using at least one of three criteria:

1. Clinical MEN1: two or more primary MEN1–associated endocrine tumors (parathyroid adenoma, enteropancreatic NET, and pituitary adenoma) in an individual patient;

TABLE 60.1 Comparison of the Different MEN Syndromes

SYNDROME NAME	MEN1	MEN2A	MEN2B	MEN4
Eponym/ other name:	Wermer's syndrome	Sipple's syndrome	MEN3	MENX
Gene:	*MEN1*	*RET*	*RET*	*CDKN1B*
Primary clinical findings:	1. Pituitary adenomas (30%–40%) 2. 1° HPTH (near 100%) 3. Pancreatic/duodenal NETs (40%–70%) Gastrinomas (40%) Insulinomas (10%) Nonfunctioning (55%) Glucagonoma and VIPoma (more rare)	1. MTC (90%–100%) 2. 1° HPTH (20%–30%) 3. PCC (50%)	1. MTC (>90%) 2. PCC (40%–50%)	1. Pituitary adenomas (30%–45%) 2. 1° HPTH (55%–80%) 3. Pancreatic/ duodenal NETs (14%–25%) Gastrinomas (33%) Nonfunctioning (66%)
Other clinical findings:	• angiofibromas (85%) • adrenal cortical tumors (usually adenoma) (40%) • PCC (<1%) • lipomas (30%) • collagenomas (70%) • foregut NETs (10%) • meningiomas (8%) • increased risk of breast cancer (controversial)		• marfanoid body habitus (40%–50%) • ocular abnormalities (enlarged corneal nerves & conjunctivitis sicca) (40%–50%) • mucosal neuromas (40%–50%)	• adrenal cortical tumors (usually adenoma) (4%–7%) • foregut NET (4%–7%)

MEN, Multiple endocrine neoplasia; *MEN1*, multiple endocrine neoplasia type 1; *MEN2A,* multiple endocrine neoplasia type 2A; *MEN2B,* multiple endocrine neoplasia type 2B; *MEN4,* multiple endocrine neoplasia type 4; *MTC,* medullary thyroid cancer; *1° HPTH*, primary hyperparathyroidism, *MTC,* medullary thyroid cancer; *NET,* neuroendocrine tumor, *PCC,* pheochromocytoma.

Adapted from Thakker RV. MEN1 and MEN4. *Mol Cell Endocrinol*. 2014;5;386(1–2):2–15; Giusti F, Marini F, Brandi ML. Multiple endocrine neoplasia type 1. 2005 Aug 31 [Updated 2022 Mar 10]. In: Adam MP, Feldman J, Mirzaa GM, et al. eds. *GeneReviews® [Internet]*. University of Washington, Seattle; 1993–2024.

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2. Familial MEN1: occurrence of one MEN1–associated tumor AND a clinical diagnosis of MEN1 in a first-degree relative; or
3. Genetic MEN1: germline pathogenic variant in *MEN1* regardless of current clinical manifestations (in other words, a genetic carrier)

7. How common is MEN1?

MEN1 has a prevalence of about 1 in 30,000 individuals (33 patients in a city of 1 million population). The prevalence of MEN1 in patients who have primary hyperparathyroidism is 1–18%, gastrinoma is 16–38% and pituitary adenoma is less than 3%. MEN1 is highly penetrant. Nearly 100% of patients with MEN1 develop biochemical evidence of primary hyperparathyroidism by age 50.

8. How does primary hyperparathyroidism differ in MEN1 versus sporadic cases?

Primary hyperparathyroidism associated with MEN1 is typically caused by four-gland hyperplasia, whereas single-gland adenomas are more frequently seen in sporadic cases (80–85%). Primary hyperparathyroidism occurs in almost all patients with MEN1. It is both the most common and earliest manifestation of MEN1. There is a higher incidence of ectopic or supernumerary glands in MEN1-associated primary hyperparathyroidism, and the degree of calcium and parathyroid hormone elevation is typically milder. The average age of onset in MEN1 is 20–25 years, and it is equally common in men and women. The average age in sporadic primary hyperparathyroidism is 50–60 years, and it is three times more common in women than in men. Compared with those who have sporadic primary hyperparathyroidism, impairment of renal function can occur earlier in those with MEN1, and bone mineral density tends to be lower in patients with MEN1–associated disease, most likely due to the earlier age of onset. Malignant transformation of the affected parathyroid glands is extremely rare.

9. What is the approach to therapy for hyperplastic parathyroid glands?

Surgical resection is the mainstay for the treatment of both sporadic parathyroid adenomas and MEN1-associated parathyroid hyperplasia. In sporadic primary hyperparathyroidism, parathyroidectomy or resection of the solitary adenoma, when indicated, is curative in 95% of cases. Because of the multiglandular hyperplasia in MEN1, subtotal parathyroidectomy (resection of at least 3.5 glands) or total parathyroidectomy (with or without autologous parathyroid reimplantation) is required to maintain eucalcemia. Concurrent transcervical thymectomy is also suggested for patients with MEN1 to remove any ectopic parathyroid glands and reduce the risk of thymic neuroendocrine development. While persistent or recurrent hypercalcemia within 10 years occurs in only 4% of patients without MEN1, this risk increases to 20–60% in patients with MEN1 despite the surgical approaches previously described. Due to the high rate of persistent/recurrent hypercalcemia and the risk of hypoparathyroidism with total or subtotal parathyroidectomy (which can be very challenging to control), surgery for hyperparathyroidism in patients with MEN1 should be delayed until complications of hypercalcemia are imminent.

10. How common is neoplastic transformation of pancreatic islet cells in MEN1?

Neoplastic transformation of the pancreatic islet cells is the second most common manifestation of MEN1. Clinically evident tumors occur in approximately 40–70% of cases, although the true incidence of all pancreatic neuroendocrine tumors (PNETS) is likely underestimated. At autopsy, microscopic PNETS are observed in 95% of patients with MEN1. Of note, many of these tumors can occur in the nearby duodenum and are sometimes referred to as gastroenteropancreatic NETs (GEP-NETS) or duodenopancreatic NETs. PNETs associated with MEN1 are often multifocal and nonfunctional. Some PNETs will secrete a hormone that contributes to a clinical syndrome (i.e., insulinoma, gastrinoma, VIPoma, somatostatinoma, and glucagonoma), but this is rare. PNETs can become metastatic with risk increasing with larger size tumors (over 2 cm). Once the tumor is metastatic and causes regional lymphadenopathy and/or liver metastases, curative resection becomes more difficult.

11. What are the most common gastroenteropancreatic tumors in MEN1?

Nonfunctioning PNETs occur in 55% of patients with MEN1. They may produce peptides and hormones (i.e., pancreatic polypeptide); however, they seldom cause specific symptoms. These tumors, and if they metastasize, the liver is a common location tend to be multifocal.

Gastrin-producing neuroendocrine tumors, also called gastrinomas which cause Zollinger-Ellison Syndrome, are the most common functional GEP-NETs in MEN1 (40% of cases). Gastrin stimulates gastric acid secretion from parietal cells and histamine secretion from enterochromaffin-like cells. Gastrin-mediated histamine release further stimulates parietal cell gastric acid production. The excess gastric acid results in peptic ulcers, gastric bleeding, diarrhea, and other gastrointestinal complications. Most gastrinomas are sporadic, but 16–38% occur in association with MEN1. Compared with sporadic tumors, most MEN1-associated gastrinomas arise in the duodenum (>70%). They also tend to be multiple, submucosal, small (<5 mm), and less likely to have metastasized to the liver at diagnosis.

Insulinomas are the second most common functional PNET in MEN1 syndrome (10% of cases). Inappropriate or unregulated insulin secretion causes severe hypoglycemia, marked by elevated serum insulin, proinsulin, and C-peptide levels. Compared to sporadic tumors, MEN1–associated insulinomas are more frequently multicentric and metastatic. Approximately 10% of all patients with an insulinoma have MEN1.

Less than 1% of MEN1 patients harbor glucagonomas, somatostatinomas, and VIPomas. In rare cases, some PNETs can have ectopic secretion of hormones such as GHRH (resulting in acromegaly), PTHrP (causing hypercalcemia), and ACTH (giving rise to ectopic Cushing's syndrome). PNETs can also secrete multiple hormones, which has been observed in approximately 1–10% of MEN1-related gastrinomas.

12. How do patients with MEN1-associated gastrinomas present?

Excessive gastrin secretion from gastrinomas, most of which occur in the duodenum, causes prolific gastric acid production. This leads to multiple duodenal and jejunal ulcers, which can become refractory to acid-lowering therapy and can lead to enlarged gastric folds and diarrhea. The diagnosis is established by demonstrating hypergastrinemia in the setting of increased basal gastric acid secretion (gastric pH <2) examined during EGD. Basal fasting serum gastrin levels usually exceed 500 pg/mL. Importantly, patients must NOT be taking proton-pump inhibitor (PPI) or histamine-2 (H2) blocker medications during assessment, as both can falsely elevate gastrin levels. Unfortunately, symptoms may be so severe that patients cannot come off these medications. Although it is seldom used, a secretin stimulation test or calcium infusion may aid in the differentiation of gastrinomas from other hypergastrinemic states. Serum gastrin levels in patients with gastrinomas increase by at least 200 pg/mL after the IV administration of secretin.

13. What other conditions cause hypergastrinemia?

Any condition that stimulates normal gastrin secretion can cause hypergastrinemia, such as hypercalcemia. Primary hyperparathyroidism can therefore elevate serum gastrin levels in patients without gastrinomas. Additionally, conditions that interfere with normal gastric acid production and feedback to the G cells can also result in elevated gastrin levels. This includes achlorhydria, gastric outlet obstruction, retained antrum with a Billroth II procedure, vagotomy, and medication use (PPI and H2 blockers). Of note, restoration of normocalcemia with the treatment of primary hyperparathyroidism may improve gastrin levels and symptoms in up to 20% of patients with MEN1-associated hypergastrinemia.

14. How are gastrinomas treated?

Because most MEN1-associated gastrinomas are small, multiple, and duodenal, surgical cure is difficult, and resection should be done by expert surgeons. Symptoms of hypergastrinemia can often be pharmacologically controlled with the use of a PPI medication at high doses and some may need the addition of an H_2 blocker. Surgical resection is indicated if the tumors are over two cm in size or have a rapid growth rate. In patients with gastrinoma, there are lymph node metastases in 70%–80% of cases and liver metastases in 25% of cases. Because gastrinomas express surface receptors for somatostatin, somatostatin-receptor scintigraphy (DOTATATE PET/CT) can be used in combination with magnetic resonance imaging (MRI)/computed tomography (CT) surveillance to monitor tumor progression.

15. Summarize the approach to the treatment of hypoglycemia associated with insulinomas.

Insulinomas can produce devastating, difficult-to-control hypoglycemia. Surgical resection of the tumor(s) is required in most patients. Localization is accomplished preoperatively with endoscopic ultrasonography, MRI/CT, Ga-68 DOTATATE PET/CT, or selective arterial calcium stimulation. The latter is rarely used and involves sequential calcium gluconate injections into the various arteries supplying the pancreas; insulin levels are sampled from the right hepatic vein following each calcium injection in order to locate the section of the pancreas where the insulinoma most likely resides. Intraoperative ultrasonography may help localize the tumor. Alternatively, endoscopic radiofrequency ablation (RFA) can sometimes treat more discreet lesions. Medical therapy, such as diazoxide, somatostatin analogs, or PRRT can be pursued for patients who are not candidates for surgery or those with metastatic/unresectable disease.

16. How do pituitary tumors originate in MEN1?

Pituitary tumors occur in 30–40% of MEN1 cases; two-thirds of these are microadenomas. These typically result from neoplastic transformation of anterior pituitary cells with clonal expansion to a tumor. While MEN1-associated pituitary adenomas have larger size, more aggressive behavior, and decreased response to therapy compared to sporadic pituitary tumors, the prevalence of pituitary carcinoma is not increased.

17. Which pituitary adenomas are most commonly associated with MEN1?

Lactotroph adenomas, or prolactinomas, are the most common pituitary tumors associated with MEN1 (60% of cases). Hyperprolactinemia symptoms include galactorrhea, oligo/amenorrhea in women, decreased libido in men, and infertility. Tumors are typically multicentric and larger than

1 cm (macroadenomas). They respond to dopamine agonists, such as cabergoline or bromocriptine. In 15% of patients with MEN1, a prolactinoma may be the first manifestation of MEN1.

The second most common pituitary tumor type is the somatotroph adenoma, or growth hormone–secreting tumor, which is reported in approximately 25% of patients. These patients have high circulating levels of growth hormone (GH) and insulin-like growth factor 1 (IGF1), leading to acromegaly, cardiac dysfunction, and colon polyps.

Less common pituitary tumors include nonfunctioning pituitary adenomas, corticotroph adenomas leading to Cushing's disease, thyrotroph adenomas leading to central hyperthyroidism, and gonadotroph adenomas.

18. Describe other endocrine tumors associated with MEN1.

About 10% of patients with MEN1 have foregut neuroendocrine tumors, previously referred to as carcinoids. These may be bronchopulmonary, thymic, or gastric in origin. Foregut NETs cause 50% of deaths in MEN1. Because most bronchial and thymic NETs generally fail to produce symptoms or synthetizes substances that can be used as tumor markers, screening is dependent on radiological imaging. Type II gastric NETs [formally called enterochromaffin-like (ECL) cell carcinoids] are associated with MEN1 and gastrinomas. They may be detected incidentally at the time of upper endoscopy.

Adrenocortical tumors are present in 40% of patients with MEN1. These are usually nonfunctioning, bilateral, and benign. Rarely, pheochromocytoma can be seen, but this is much less common compared to MEN2 syndromes.

19. Are there any nonendocrine tumors associated with MEN1?

Yes. Facial angiofibromas and collagenomas, subcutaneous or visceral lipomas, and meningiomas are frequently found in MEN1 patients.

20. Does MEN1 increase the risk of breast cancer?

One study reported that females with MEN1 had a 2.8-fold increased risk of breast cancer, which was diagnosed about 15 years earlier than in females without MEN1. Several other studies have since supported this finding, although causality is still unclear. While formal recommendations do not exist, it is prudent to begin annual mammography at age 40 years in females with MEN1.

21. Who should receive genetic testing for MEN1?

Patients with a clinical diagnosis of MEN1, first-degree relatives of patients with known MEN1, and individuals with atypical MEN1-associated tumors should receive genetic testing. Atypical MEN1-associated tumor presentations include parathyroid adenoma when <30 years old, multiglandular parathyroid disease, multiple PNETs, gastrinoma, or ≥2 of the less classic MEN1-associated tumors (adrenal tumor, angiofibroma, foregut NET, etc.).

Sequencing and deletion/duplication testing of the *MEN1* gene is the first-line test. This should be done in conjunction with genetic counseling consultation. If genetic panel testing returns negative yet the clinical suspicion is high, further testing can be done.

22. What is the approach for screening in patients who have MEN1?

Asymptomatic carriers of the MEN1 mutation should be screened for biochemical and anatomic evidence of tumors. Manifestations of MEN1 syndrome have been reported as early as 5 years of age; therefore, patients at risk should consider starting endocrine screening at that time. Nearly all people at risk for MEN1, develop the disorder by the age of 40 years. See Table 60.2.

23. What are the common and distinguishing features of MEN2A and MEN2B?

RET (REarranged during Transfection) germline pathogenic variants and the presence of medullary thyroid cancer (MTC) are the defining features of MEN2 syndromes. Most patients with MEN2 will develop MTC in their lifetime with different age-related penetrance based on the *RET* codon altered. MEN2A comprises 95% of MEN2 syndromes and MEN2B accounts for the other 5%. See Table 60.1.

MEN2A is subdivided into four categories:

1. Classic MEN2A: All patients develop MTC. Hyperparathyroidism tends to be mild. Pheochromocytoma (PCC) tends to be bilateral, multicentric, and confined to the adrenal gland.

TABLE 60.2 Overview of Screening for Patients With MEN1 Syndrome

GENE	CLINICAL FEATURES	FREQUENCY	SCREENING	AGE TO INITIATE SCREENING
MEN1	**Primary findings**			
	1. Anterior pituitary adenoma	30–40%	Brain MRI (q3 years) • Prolactin & IGF-1 (annual)	Age 5 years
			Other pituitary hormones: based on signs, symptoms, or tumor size (>1 cm)	Symptom-dependent
	2. 1° HPTH	>95%	Calcium level with PTH & vit D (annual)	Age 8 years
			Abdominal CT or MRI (annual)	Age 10 years
	3. Pancreatic/duodenal NETs	40–70%	• Chromogranin A, glucagon, pancreatic polypeptide, VIP (annual)	Age <10 years
			• Insulin, proinsulin, & fasting BG (annual)	Age <5 years
			• Fasting gastrin (annual)	Age 20 years
	Additional findings			
	• angiofibromas	85%	NA	
	• adrenal cortex tumors	40%	Monitor on annual abdominal CT or MRI for PNETs	Age 10 years
	• lipomas	30%	NA	
	• collagenomas	70%	NA	
	• foregut NETs	10%	CT/MRI chest + abdomen (every 1–2 years)	Age 15 years
	• meningiomas (8%)	8%	NA	
	• breast cancer	2.8 x risk	Mammography (annual)	Age 40 years

MEN1, Multiple endocrine neoplasia 1; *1° HPTH,* primary hyperparathyroidism; *PTH,* parathyroidism; *VIP, BG,* blood sugar; vasoactive intestinal peptide; *MRI,* magnetic resonance imaging; *CT,* computed tomography; *PNETs,* pancreatic neuroendocrine tumors; *NETs,* neuroendocrine tumors
Adapted from Thakker RV. Clinical practice guidelines for MEN1. *J Clin Endocrinol Metab.* 2021;97(9):2990–3011. Please note that new MEN1 guidelines are in process and should be published soon.

2. MEN2A with Cutaneous Lichen Amyloidosis: Patients feel pruritus with stress and sun exposure, and hyperpigmented lesions occur mostly in the T2–T6 dermatomes.
3. MEN2A with Hirschsprung's disease: Hirschsprung's disease presents shortly after birth.
4. Familial MTC: MTC only; no pheochromocytoma/paraganglioma (PCC/PGL) or primary hyperparathyroidism.

MEN2B is aggressive and typically presents in infancy or childhood. Seventy-five percent of MEN2B mutations are *de novo*. PCC develops in 50% of affected individuals.

24. What causes MEN2A?

MEN2A is caused by an activating germline pathogenic variant of the *RET*, protooncogene, which is located on chromosome 10q11.2 and has 21 exons. The RET protein is a transmembrane receptor tyrosine kinase that transduces growth and differentiation signals in several developing tissues, including those derived from the neural crest. Normal ligand-mediated activation of this receptor results in dimerization of the RET protein, autophosphorylation, and phosphorylation of intracellular substrates. The *RET* gene mutation results in constitutive activation of the RET protein, causing unregulated phosphorylation of other critical proteins expressed in the thyroid C-cells, adrenal medulla, and in other tissues. Inheritance follows an autosomal dominant pattern.

25. How is MEN2 diagnosed?

Diagnosis of MEN2 is made predominantly through genetic testing in individuals with characteristic clinical findings, like MTC and/or PCC. Rarely, families will exhibit findings of classical MEN2A without an identifiable *RET* mutation. The diagnosis can be made clinically if at least one first-degree relative also has the clinical syndrome of classic MEN2A.

26. How common is MEN2?

MEN2 affects 1 in 30,000 individuals (33 patients in a city of 1 million population). MEN2A accounts for 95% of cases while MEN2B accounts for 5%.

27. How does MTC differ between MEN2–associated and sporadic cases?

MTC results from the malignant transformation of the parafollicular cells (or C cells) that normally secrete calcitonin and are scattered throughout the thyroid gland. MTC accounts for 4–5%

of all thyroid malignancies. Sporadic MTC is more common (75% of all cases) and tends to arise in older individuals (peak age: 40–60 years). It occurs in a solitary form (>80% of cases), and metastasizes early in the disease (lymph nodes, lung, bone, and liver).

Unlike sporadic MTC, parafollicular cells in patients with MEN2A progress through a state of C-cell hyperplasia to nodular hyperplasia to malignant degeneration over a variable period of time. MEN2A-associated MTC occurs at a much younger age (even in early childhood), is often multifocal (90% at the time of diagnosis), and generally has a better prognosis than the sporadic form. MTC occurs in virtually all cases of MEN2A and is usually the first tumor to appear.

28. What are the symptoms of MTC?

Most patients present with one or more palpable thyroid nodules, cervical lymphadenopathy, or incidentally found thyroid nodules on imaging studies. Clinical manifestations of MEN2–associated MTC do not differ from the sporadic version.

Calcitonin, calcitonin gene–related peptide, or other substances secreted by MTC tumors may cause diarrhea or facial flushing. The associated diarrhea is secretory and affects 4–7% of patients at diagnosis but develops in 25–30% of patients over time.

About 3% of patients with MTC can develop Cushing's syndrome due to ectopic ACTH secretion by the tumor.

29. How is MEN2A-associated MTC treated?

It is imperative that at-risk patients be diagnosed while in the C-cell hyperplasia stage or before any changes occur. Early total thyroidectomy is recommended to prevent MTC development and metastasis. If MTC has already developed, a total thyroidectomy with bilateral central neck node dissection is the treatment of choice.

30. Is C-cell hyperplasia pathognomonic of MEN2?

No. Secondary C-cell hyperplasia, which is not a premalignant lesion, occurs with aging, hypergastrinemia, hyperparathyroidism, and Hashimoto's thyroiditis.

31. What is the second most common neoplasm associated with MEN2A?

PCCs develop in up to 50% of patients with MEN2A and are bilateral in two-third of cases. They are usually benign and rarely extra-adrenal. Compared with the sporadic form, MEN2A–associated PCCs secrete greater amounts of epinephrine compared with norepinephrine. Hypertension is therefore less common (30% of cases). Because 5% of sporadic cases of MTC are associated with *RET* mutations, screening for coexistent PCC is mandatory before thyroidectomy for anyone with MTC.

32. Summarize the treatment of pheochromocytoma associated with MEN2A.

Laparoscopic surgical resection is indicated for MEN2–associated PCC after appropriate alpha blockade. Cortical sparing surgery is possible, especially for someone with bilateral pheochromocytoma and a genetic predisposition, to help prevent primary adrenal insufficiency from bilateral adrenalectomy. There is a low risk for recurrence in the remaining adrenal tissue.

33. Is the hyperparathyroidism associated with MEN2a similar to that found in MEN1?

Yes, but it is much less common, involving 20–30% of cases. There is more often an adenoma instead of four gland hyperplasia as seen in MEN1.

34. Describe MEN2A screening and surveillance.

The risk for MTC is based on the *RET* germline pathogenic variant identified (see next section). Screening for MEN2A–associated pheochromocytoma should be performed annually by measuring plasma or urinary fractionated metanephrines starting by age 11 years in carriers of high-risk *RET* germline pathogenic variants and by age 16 years in moderate-risk *RET* germline pathogenic variants. Serum levels of albumin-corrected calcium or ionized calcium should be assessed annually MEN2A. See Table 60.3.

35. When should thyroidectomy be pursued in MEN2A and MEN2B?

The decision for prophylactic thyroidectomy is based on the American Thyroid Association risk categorization for aggressive MTC based on individual *RET* germline pathogenic variants. Because C-cell hyperplasia has been described in high-risk gene carriers as young as 2 years, total thyroidectomy is

TABLE 60.3 Overview of Screening for Patients With MEN2A Syndrome

GENE	CLINICAL FEATURES	FREQUENCY	SCREENING/PROPHYLACTIC MEASURES	AGE TO INITIATE SCREENING
RET	**Primary findings**			
	1. Medullary thyroid cancer	90–100%	High risk variant: thyroidectomy	Age <5 years
			Moderate risk variant: thyroidectomy or monitor with labs every 6–12 months	Age <5 years
			High or Moderate risk: annual calcitonin (± CEA)	Age <3–5 years
	2. Primary hyperparathyroidism	20–30%	High risk variant: Ca, albumin, PTH (annual)	Age 11 years
			Moderate risk variant: Ca, albumin, PTH (annual)	Age 16 years
			If thyroidectomy pursued: Ca, albumin	Preop
	3. Pheochromocytoma	50%	High-risk variant: plasma metanephrines (annual)	Age <11 years
			Moderate-risk variant: plasma metanephrines (annual)	Age <16 years
			Before any pregnancy or surgery: plasma metanephrines	Preop

PTH, parathyroidism; *RET*, REarranged during Transfection, *CEA*, carcinoembryonic antigen.
Adapted from Eng C, Plitt G. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2023 Aug 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2025.
Available from: https://www.ncbi.nlm.nih.gov/books/NBK1257/.

TABLE 60.4 Suggested Age for Prophylactic Thyroidectomy Based on RET Variant

RET MUTATIONS	RISK	PROPHYLACTIC THYROIDECTOMY
918	Highest risk	Within first year of life
634, 883	High risk	Before age 5 years
609, 611, 618, 620, 630, 768, 790, 804, 891	Moderate risk	Consider before age 5 years Can trend calcitonin or pursue other monitoring tests to decide on surgical timing

RET, REarranged during Transfection
Adapted from McDonnell JE, Gild ML, Clifton-Bligh RJ, Robinson BG. Multiple endocrine neoplasia: an update. *Intern Med J.* 2019;49(8):954–961. PMID: 31387156.

suggested in affected individuals before age 5 years. For some codons with lower-risk penetrance, care can be individualized as shown in Table 60.4. For lower-risk *RET* germline pathogenic variants or patients opting for surveillance over surgery, as long as there are no known thyroid nodules, calcitonin plus carcinoembryonic antigen (CEA) can be monitored every 6–12 months.

36. What comprises the MEN2B syndrome?

MEN2B syndrome refers to the constellation of MTC, PCC, and multiple mucosal neuromas. These neuromas can occur at the distal tongue, lips, eyelids, and gastrointestinal tract. When seen on the exam, they should always raise suspicion for MEN2B. Other manifestations include marfanoid body habitus without ectopia lentis or vascular aneurysms, hypertrophic corneal nerves, and slipped femoral epiphysis. Primary hyperparathyroidism is not observed. See Table 60.1. This syndrome is less common than the MEN2A.

More than 95% of patients with MEN2B carry a *RET* germline pathogenic variant at codon 918 (exon 16) which codes for a methionine-to-threonine substitution. This mutation confers the highest risk of developing MTC (see Table 60.4).

37. How should MEN2B be followed and treated?

MEN2B–associated MTC is more aggressive than other forms, as metastatic lesions have been described in infancy. Given the risk of early metastasis, many experts recommend that affected children undergo total thyroidectomy as soon as surgery can be tolerated. See Tables 60.4 and 60.5. PCC occurs in 50% of patients and follows a clinical course similar to MEN2A syndrome.

TABLE 60.5 Overview of Screening for Patients With MEN2B Syndrome

GENE	CLINICAL FEATURES	FREQUENCY	SCREENING/PROPHYLACTIC MEASURES	AGE TO INITIATE
RET	**Primary findings**			
	1. Medullary thyroid cancer	>90%	Highest-risk variant: thyroidectomy	Age <1 year
			High-risk or moderate-risk variant: thyroidectomy	Age <5 years
	2. Pheochromocytoma	40–50%	Calcitonin & CEA (annual)	Age <3 years
			If thyroidectomy pursued:	Preop
			High-risk variant: plasma metanephrines (annual)	Age <11 years
			Moderate-risk variant: plasma metanephrines (annual)	Age <16 years
	Additional findings			
	• marfanoid body habitus (40–50%)	40–50%	NA	
	• ocular abnormalities: enlarged corneal nerves & conjunctivitis sicca	40–50%	NA	
	• mucosal neuromas	40–50%	Na	

MEN2, Multiple endocrine neoplasia type 2, *RET*, REarranged during Transfection; *CEA,* carcinoembryonic antigen.
Adapted from Eng C, Plitt G. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2023 Aug 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1257/. [Updated 2023 Aug 10]

38. How should family members be screened after the identification of an individual with MEN syndrome?

Familial cascade genetic testing should be pursued once an individual is identified with MEN1, MEN2A, or MEN2B. This involves notification of the individual's blood relatives at risk of having the same mutation and inviting them for targeted genetic testing for the same germline pathogenic variant. Screening should be conducted with assistance from a genetic counselor.

39. What is MEN4?

MEN4 describes a small group of patients who appear to have the clinical syndrome of MEN1 but with a germline pathogenic variant in the *CDKN1B* gene instead of *MEN1. CDKN1B* is located on chromosome 12p13.1 and encodes the 198 amino acid cyclin-dependent kinase inhibitor (CK1). This protein regulates cell motility and apoptosis. About 3% of patients with MEN1-associated tumors, such as parathyroid adenomas, PNETs, and pituitary adenomas actually have MEN4. See Table 60.1 for details.

KEY POINTS

MEN1

- MEN1 consists of hyperplasia or neoplastic transformation in at least two of these three glands: parathyroid glands, pancreas, and anterior pituitary.
- MEN1 results from a germline pathogenic variant inactivating the *MEN1* tumor suppressor gene on chromosome 11 which encodes the protein Menin. Routine clinical testing for the mutation is currently available.
- Therapy for MEN1 includes surgical resection of hyperplastic parathyroid tissue and pituitary adenomas; surgical cure for associated gastroenteropancreatic tumors, which are multiple and frequently metastatic, can be difficult without full pancreatectomy, therefore, surgery is considered typically for large or growing tumors.
- Although patients with MEN1 have decreased life expectancy, presymptomatic tumor detection may improve the prognosis for these patients.

KEY POINTS

MEN2A and MEN2B

- MEN2A consists of neoplastic transformation of parathyroid glands, thyroid parafollicular C cells, and the adrenal medulla.
- MEN2B consists of neoplastic transformation of thyroid parafollicular C cells and the adrenal medulla, with mucosal neuromas and marfanoid body habitus.
- Genetic testing for *RET* germline pathogenic variants to rule in or rule out MEN2 should be offered to all patients diagnosed with MTC.

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CHAPTER 61

Pancreatic Neuroendocrine Tumors

Michael T. McDermott

1. What are pancreatic neuroendocrine tumors?

Pancreatic neuroendocrine tumors (PNETs) arise in the pancreas, most often in the Islets of Langerhans, and account for 1–2% of all pancreatic tumors. PNETs (50–75%) are most often nonfunctioning (50–75%)—no hormone production or no clinical hormone excess syndrome. Functioning PNETs are named for the hormones they secrete: insulinomas, gastrinomas, glucagonomas, somatostatinomas, and vasoactive intestinal polypeptide tumors (VIPomas). PNETs can also secrete adrenocorticotropic hormone (ACTH), corticotropin-releasing factor (CRF), and growth hormone–releasing factor (GRF) (Fig. 61.1).

2. How do people with nonfunctioning PNETS present?

Nonfunctioning PNETs are often discovered incidentally on abdominal imaging done for other reasons. When symptomatic, abdominal pain (35–78%), weight loss (20–35%), anorexia/nausea (45%), obstructive jaundice (17–50%), intraabdominal hemorrhage (4–20%), and a palpable mass (7–40%) are the most common presenting issues. Metastases have been reported in 32–73% at diagnosis. People with PNETs initially considered to be nonfunctional may later develop symptoms of excess hormone secretion.

3. Are PNETS usually benign or malignant?

Insulinomas are usually benign (80–90%), but severe hypoglycemia due to excess insulin secretion can be potentially fatal. Other PNETs are more often malignant/metastatic (50–80%). The proliferative index (Ki-67 + mitoses) assigns PNET histologic grades (2017 WHO PNET classification). A G3 category (Ki-67 > 20%) is very concerning and requires more intensive investigation and monitoring.

4. Are PNETS associated with other endocrine disorders?

PNETs are usually sporadic but can be part of inherited endocrine tumor syndromes such as multiple endocrine neoplasia type 1 (MEN-1), Von Hippel Lindau (VHL) syndrome, and Neurofibromatosis type 1 (NF-1). PNETs occur in approximately 80–100% of people with MEN-1, approximately 20% of people with VHL, and approximately 10% of those with NF-1. PNETs also occur in approximately 1% of people with tuberous sclerosis.

5. What are insulinomas?

Insulinomas are single or multiple insulin-producing tumors arising from pancreatic beta cells; they must be distinguished from other hyperinsulinemic disorders: exogenous insulin or insulin secretagogue (sulfonylurea, meglitinide) administration, islet cell hyperplasia, noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), postgastric bypass hypoglycemia (PGPH), and nesidioblastosis (neoproliferation of beta cells along the pancreatic ducts).

6. What is Whipple's triad?

- Hypoglycemia (documented <55 mg/dl)
- Symptoms during hypoglycemia
- Relief of symptoms with correction of hypoglycemia

7. What are the symptoms of hypoglycemia?

Hypoglycemia is classified by symptom type and relation to meals. Neuroglycopenic symptoms (confusion, slurred speech, blurred vision, seizures, coma) result from inadequate brain glucose delivery. Adrenergic symptoms (tremors, sweating, palpitations, nausea) result from catecholamine discharges. Symptoms occurring within 4–5 hours of a meal are "postprandial;" those occurring more than 5 hours after meals are considered "fasting."

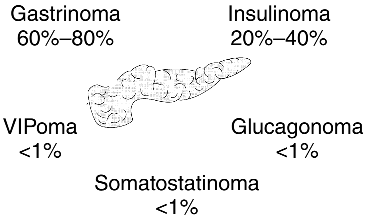

Fig. 61.1 Pancreatic islet cell tumors.

TABLE 61.1 Diagnostic Criteria for Insulinoma: Demonstration of Hypoglycemia With Endogenous Hyperinsulinemia

TEST	THRESHOLD	SENSITIVITY	SPECIFICITY*
Glucose	<55 mg/dl		
Insulin	≥3 uU/ml	93%	95%
C-Peptide	≥0.6 ng/ml	100%	60%
Proinsulin	≥5 pmol/L	100%	68%
Beta-Hydroxybutyrate	≤2.7 mmol/L	100%	100%
Glucose rise after Glucagon	≥25 mg/dl	91%	95%
Insulin Antibodies	Negative		
Sulfonylurea Screen	Negative		
Meglitinide Screen	Negative		

*Compared to normal controls who developed glucose <60 mg/dl during a 72-hour fast.

Insulinomas most commonly cause fasting hypoglycemia (73%), but both fasting and postprandial hypoglycemia (21%) and pure postprandial hypoglycemia (6%) may be seen.

8. What evaluation is recommended to detect an insulinoma?

Blood samples obtained during an episode of witnessed hypoglycemia are very helpful, but more often the conditions that provoke the hypoglycemia must be replicated. This is most commonly done with a prolonged fast (supervised 72-hour fast or screening outpatient 12–18-hour fast). Patients are allowed to drink calorie-free, caffeine-free beverages only. Blood is drawn every 6 hours until the glucose is <60 mg/dl, then every 1–2 hours. Sufficient blood is obtained to measure glucose, insulin, c-peptide, proinsulin, and beta-hydroxybutyrate; glucose is measured immediately on all samples, and the other tests are run only on samples for which the glucose is <55 mg/dl. Insulin antibodies and serum or urine sulfonylurea and meglitinide screens are ordered on one sample. The test is stopped when typical symptoms occur when the glucose level is <55 mg/dl (if Whipple's triad was previously demonstrated) or <45 mg/dl (if Whipple's triad was not previously demonstrated) or at the end of 72 hours. At the end of the test, glucagon 1 mg is given IV, and glucose is measured 10, 20, and 30 minutes later.

9. What are the diagnostic criteria for an insulinoma?

Hypoglycemia with endogenous hyperinsulinemia must be demonstrated to diagnose an insulinoma. Diagnostic criteria are shown in Table 61.1.

10. What is the best way to localize an insulinoma?

Cross-sectional imaging of the pancreas with computed tomography (CT) or magnetic resonance imaging (MRI) is the best initial localization procedure; reported sensitivities vary from 15–90%. Endoscopic ultrasound of the pancreas has higher sensitivity (56–93%) and can detect tumors as small as 2–3 mm in size. Intraarterial pancreatic calcium infusions with measurement of insulin increments in the right hepatic vein yield similar or superior results but are more invasive.

Intraoperative ultrasound is highly accurate and useful for finding small tumors that could not be localized preoperatively. Cross-sectional imaging is also the best modality to find metastatic disease, since metastatic spread from malignant insulinomas is usually to the liver and regional lymph nodes.

11. What is the treatment for an insulinoma?

Surgery is the treatment of choice. When surgery is not desired or feasible, symptom relief can sometimes be achieved with dietary management (multiple small meals per day) and medical therapy to inhibit insulin secretion with diazoxide, somatostatin analogs (Octreotide LAR, Lanreotide, Pasireotide) or calcium channel blockers. Malignant insulinomas can show partial responses to cytotoxic chemotherapy (streptozotocin with doxorubicin or 5-fluorouracil). Other considerations may include everolimus, an inhibitor of mTOR (mechanistic target of rapamycin), sunitinib, other VEGF-R (vascular endothelial growth factor receptor) inhibitors, and peptide receptor radioligand therapy (PRRT) using radiolabeled somatostatin analogs such as 177-Lu Dotatate, 90-Y edotreotide, or 90-Y Dota tyr3-octreotide.

12. What are the clinical features of gastrinomas?

Gastrinomas secrete excessive gastrin, which stimulates prolific gastric acid secretion. Affected people develop severe peptic ulcer disease, often with secretory diarrhea. This disorder is also known as the Zollinger-Ellison syndrome.

13. Where are gastrinomas usually located?

Gastrinomas usually develop in the duodenum (70%) or the pancreatic islets (25%).

14. How is the diagnosis of gastrinoma made?

Gastrinomas are diagnosed by demonstrating a fasting serum gastrin level >1000 pg/mL associated with high gastric acidity (pH $\leq$4.0). For moderately elevated serum gastrin levels (110–1000 pg/mL), a secretin test can be conducted. A gastrin increment of $\geq$200 pg/mL 15 minutes after IV secretin administration is also diagnostic. People should be off proton pump inhibitor therapy for 1 week prior to testing for gastrinomas.

15. What is the best way to localize a gastrinoma?

Gastrinoma localization may be pursued with CT, MRI, endoscopic ultrasonography, somatostatin receptor–based functional imaging (68-Ga Dotatate or In-111 Pentetreotide), transhepatic portal venous sampling, and selective arterial secretin infusions with right hepatic vein gastrin measurements.

16. How are gastrinomas managed?

Most benign and some malignant gastrinomas can be cured by surgery. Otherwise, attention should be directed toward reducing gastric acid overproduction and secretory diarrhea. Proton pump inhibitors (high doses) are the best medications. Somatostatin analogs (Octreotide LAR, Lanreotide) are also effective agents. High-dose histamine-2 blockers may be useful but are rarely adequate by themselves. Refractory patients may require total gastrectomy and vagotomy for symptom relief.

17. How do you treat malignant gastrinomas?

Gastrinomas are often malignant, and therefore antitumor therapy is usually necessary. Since liver metastases are common, hepatic-directed therapies such as partial resection, hepatic artery embolization, and liver transplantation may be considered. Streptozotocin/Doxorubicin combination therapy is the most commonly used cytotoxic regimen for malignant pancreatic endocrine tumors. Other potential approaches that have some success include everolimus, an inhibitor of mTOR (mechanistic target of rapamycin), sunitinib, other VEGF-R inhibitors, and PRRT with 177-Lu Dotatate, 90-Y edotreotide, or 90-Y Dota tyr3-octreotide.

18. What are the characteristics of glucagonomas?

Glucagon antagonizes insulin action in the liver by stimulating both glycogenolysis and gluconeogenesis. Glucagonomas cause diabetes mellitus, weight loss, anemia, and a characteristic skin rash—necrolytic migratory erythema (NME)—as well as a high risk of thromboembolic events. The diagnosis is made by finding a significantly elevated serum glucagon level (>500 pg/mL); however, some glucagonomas show only modest hyperglucagonemia. In these cases, one must rule out other causes of mild to moderate glucagon elevations such as fasting, hypoglycemia, renal failure, liver failure, pancreatitis, sepsis, and trauma. Techniques similar to those used for gastrinomas are useful for localization.

19. How are glucagonomas treated?

Treatment options include surgery for localized disease, somatostatin analogs (Octreotide LAR, Lanreotide) to reduce glucagon secretion, hepatic-directed therapies, chemotherapy, and PRRT similar to those used for other PNETs. Chronic anticoagulation should also be considered. Zinc supplements and amino acid infusions may help reduce NME and improve the person's overall sense of well-being.

20. What are the features of somatostatinomas?

Somatostatin inhibits the secretion of insulin, pancreatic enzymes, gastric acid, and gallbladder contraction. Somatostatinomas secrete excess somatostatin, causing diabetes mellitus, weight loss, steatorrhea, hypochlorhydria, and cholelithiasis. The diagnosis is made by a significantly elevated serum somatostatin level.

21. What is the treatment for somatostatinomas?

Surgery is the treatment of choice. When surgery is not possible, the same general treatment options as discussed above for gastrinomas should be considered. However, somatostatin analog therapy (Octreotide LAR, Lanreotide) should be avoided.

22. What are the characteristics of VIPomas?

VIPomas cause watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). The diagnosis is made by finding a significantly elevated serum VIP level. This is also known as the Verner-Morrison syndrome or pancreatic cholera.

23. How are VIPomas treated?

Surgery is the treatment of choice. Somatostatin analogs effectively reduce diarrhea in most patients. Radiation therapy, chemotherapy, and PRRT also may reduce diarrhea and tumor size.

24. Briefly discuss the less common PNETs.

Other PNETs are rare. ACTH- and CRF-secreting tumors lead to the development of Cushing's syndrome, and GRF-secreting tumors cause acromegaly. Localization procedures and treatments are similar to those described for the other PNETs.

25. Explain somatostatin-receptor-based pnet imaging.

Somatostatin receptors are expressed on most well-differentiated PNETS. This has led to the development of somatostatin receptor–based whole-body imaging, which is especially effective when combined with PET/CT. 68-Ga Dotatate, 68-Ga Dotatoc, and Cu-64 Dotatate have a high affinity for somatostatin receptor subtype 2 (SSTR2), which is expressed on many PNETs. These agents are now preferred over 111-In Pentreotide because of superior sensitivity and spatial resolution. Insulinomas and poorly differentiated PNETs do not express significant SSTR2, making somatostatin receptor–based imaging less useful in these PNET types. High uptake on somatostatin receptor–based imaging also predicts a favorable response to peptide receptor radionuclide therapy (PRRT).

26. What is theranostics?

Theranostics uses diagnostic imaging to identify a molecule of interest in cancer cells with subsequent development of a precision radionuclide therapeutic that targets that molecule. A classic theranostic is radioactive iodine, I-131, which has been used since the 1940s to evaluate and treat thyroid cancer. Somatostatin receptor–based imaging followed by PRRT now has a significant role in the treatment of advanced PNETs.

27. What theranostic agents are currently used to treat PNETS?

PRRT with 177Lu-Dotatate (Luthera) can be considered for the treatment of persistent, progressive, and metastatic PNETs. 177Lu-Dotatate has a high affinity for somatostatin receptors and emits gamma radiation to allow post-therapy distribution scans. Beneficial responses have been reported in the majority of treated patients; high uptake on somatostatin receptor–based imaging correlates well with tumor regression.

KEY POINTS

- PNETs insulinomas usually cause fasting hypoglycemia with neuroglycopenic symptoms; diagnosis requires demonstrating true hypoglycemia with concomitant nonsuppressed serum insulin and c-peptide (or proinsulin), low or absent beta-hydroxybutyrate, and a negative screen for sulfonylureas and meglitinides.
- Gastrinomas (Zollinger-Ellison syndrome) cause aggressive peptic ulcer disease, often associated with secretory diarrhea; diagnosis involves finding a markedly elevated serum gastrin or a prominent increase in gastrin after intravenous secretin administration in a patient with proven gastric acidity.
- Insulinomas, the most common type of PNET, are usually benign, but other PNETs are more often malignant, with the liver being the most common site of metastases.
- Somatostatin receptor–based imaging and peptide receptor radionuclide therapy (PRRT) have been major additions to our ability to monitor and treat advanced PNETs.

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CHAPTER 62

Carcinoid Syndrome and Carcinoid Crisis

Michael T. McDermott

1. What are carcinoid tumors and how are they classified?

Carcinoid tumors arise from enterochromaffin cells. A more common term is neuroendocrine tumors (NETs). NETs are classified according to the site of origin: foregut (bronchus, stomach, duodenum, bile ducts, pancreas), midgut (jejunum, ileum, appendix, cecum, ascending colon), or hindgut (transverse and descending colon, rectum) NETs. Pulmonary NETs are still often referred to as carcinoids, but the term NET has been proposed by the World Health Organization (WHO) for NETs in other locations. NETs less commonly develop in the ovaries, testes, prostate, kidney, breast, thymus, or skin. Approximately 55% of NETs occur in the gastrointestinal (GI) tract and 30% are found in the bronchopulmonary system. Malignant NETs are referred to as neuroendocrine carcinomas.

2. Define carcinoid syndrome.

Carcinoid syndrome is a group of symptoms that occur when NETs secrete large amounts of various humoral substances into the systemic circulation. The most common features are cutaneous flushing (85–90%), secretory diarrhea (75–80%), bronchospasm (10–20%), fibrotic growths of the endocardium and right heart valves (33%), and sometimes pleural, peritoneal, or retroperitoneal fibrosis. Carcinoid syndrome may also cause hypotension, especially during prolonged flushing spells. Carcinoid syndrome most often results from midgut NETs (jejunum, ileum, appendix, cecum, ascending colon) that have metastasized to the liver. Carcinoid syndrome is rarely associated with foregut and hindgut NETs.

3. Describe the flushing that occurs in carcinoid syndrome.

The carcinoid flush that occurs with midgut NETS is characterized by sudden episodes of reddish to purplish flushing of the face, neck, and chest associated with cutaneous burning lasting anywhere from 30 seconds to 30 minutes. More severe or prolonged flushing episodes may be associated with hypotension and tachycardia. Telangiectasias eventually develop on the malar areas, nose, and upper lip due to prolonged vasodilation in the cutaneous vasculature.

Gastric NET flushing is more often patchy, serpiginous, bright red, and intensely pruritic. Pulmonary NET flushing can be prolonged (hours to days) and more severe and may be associated with hypotension, tachycardia, anxiety, disorientation, periorbital edema, lacrimation, salivation, dyspnea, wheezing, and diarrhea.

4. What are the biochemical mediators of carcinoid syndrome?

Carcinoid syndrome results from humoral mediators secreted by NETs that reach the systemic circulation. Carcinoid syndrome does not usually occur with midgut NETs unless there are extensive liver metastases that impair mediator metabolism or secrete mediators directly into the circulation via the hepatic vein. Extraintestinal NETs may cause carcinoid syndrome without liver metastases, since mediators from these tumors are not secreted into the portal veins.

The most important humoral mediators are serotonin, histamine, kallikrein, bradykinin, tachykinins, and prostaglandins (Fig. 62.1). Histamine is the main mediator of flushing; kallikrein, bradykinin, and tachykinins may also contribute. Serotonin is the primary mediator of diarrhea and fibrous tissue formation in the heart, serosal tissues (pleural, peritoneal), and retroperitoneal spaces; kinins and prostaglandins may also contribute to secretory diarrhea. The formation and metabolism of serotonin are shown in Fig 62.2.

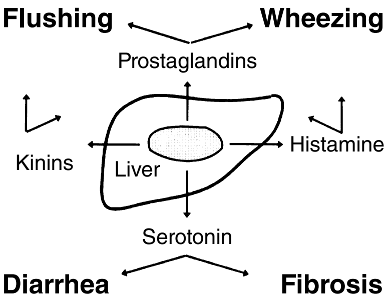
Flushing
Wheezing
Prostaglandins
Kinins
Liver
Histamine
Serotonin
Diarrhea
Fibrosis

Fig. 62.1 Carcinoid syndrome.

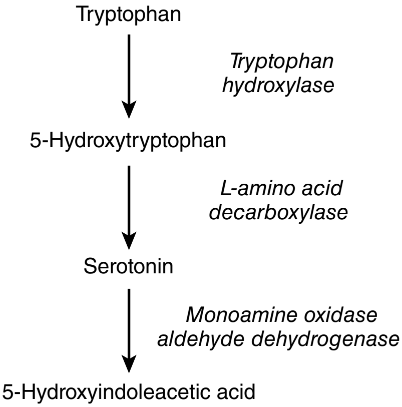
Tryptophan
Tryptophan hydroxylase
5-Hydroxytryptophan
L-amino acid decarboxylase
Serotonin
Monoamine oxidase aldehyde dehydrogenase
5-Hydroxyindoleacetic acid

Fig. 62.2 Serotonin metabolism.

5. Why do niacin deficiency and pellagra often accompany carcinoid syndrome?

Niacin deficiency occurs in carcinoid syndrome because large amounts of tryptophan are diverted from niacin synthesis to produce serotonin (Fig 62.2). This can result in classic features of pellagra: glossitis, angular stomatitis, rough scaly skin, mental confusion, and hypoproteinemia.

6. Do NETs cause any other humoral syndromes?

NETs may also secrete corticotropin-releasing factor (CRF) or adrenocorticotropin (ACTH), causing Cushing's syndrome, or growth hormone-releasing factor (GRF), causing acromegaly. These syndromes have been reported mainly with bronchial and pancreatic carcinoid tumors.

7. How is the diagnosis of carcinoid syndrome made?

Carcinoid syndrome due to midgut NETs (jejunum, ileum, appendix, cecum, ascending colon) is diagnosed by demonstrating markedly elevated 24-hour urine 5-hydroxyindoleacetic acid (5 HIAA) excretion; 5 HIAA is a metabolite of serotonin (Fig 62.2). Normal 5 HIAA excretion is <8 mg/24 hr. Causes of mild to moderate 5 HIAA elevations are shown in Table 62.1; excretion of 5 HIAA is usually <30 mg/24 hr in these situations. In carcinoid syndrome urine 5 HIAA is usually >100 mg/24 hr, although mild elevations are seen in some patients. Patients should avoid foods that are rich in tryptophan and/or serotonin and medications that can produce falsely positive or negative 5 HIAA results for 3 days prior to and on the day of collection of the 24-hour urine specimen (Table 62.1).

8. How is carcinoid syndrome diagnosed if urinary 5 HIAA is normal?

Foregut NETs typically lack the L-amino acid decarboxylase enzyme that converts 5 hydroxytryptophan to serotonin; therefore, serotonin and 5 HIAA values are usually normal (Fig 62.2). Assays

TABLE 62.1 Causes of Abnormal 5 HIAA Excretion Other Than Carcinoid Syndrome

Diseases: MALABSORPTION DISORDERS
Food (Tryptophan Rich): Bananas, Pineapples, Kiwi, Plums, Avocados, Eggplant, Pecans, Walnuts, Hickory Nuts
Medications that Increase 5 HIAA: Acetaminophen, Ephedrine, Guaifenesin, Mephenisin, Methocarbamol, Phenacetin, Caffeine, Nicotine, Methamphetamine, Phenobarbital, Acetanelid, Reserpine, Phentolamine, Phenmetrizine, Coumaric Acid, Melphalan, Fluorouracil

5 HIAA, 5 Hydroxyindoleacetic Acid

for 5 hydroxytryptophan are not available. Whole-blood serotonin, platelet-rich plasma serotonin, and urine serotonin assays are available, but their performance characteristics have not yet been established; accordingly, they are not recommended as routine screening tools but may still be useful in select patients. Similarly, a plasma 5 HIAA assay has been developed, but its usefulness for diagnosing carcinoid syndrome has not been well evaluated and the test itself is not widely available.

Chromogranins A, B, and C are secreted by multiple types of NETs. Chromogranin A is often significantly elevated in carcinoid syndrome, but there are numerous other conditions and medications (especially proton pump inhibitors) that can elevate serum chromogranin A levels. Because elevations are nonspecific, serum chromogranin A is not recommended as a routine screening test for carcinoid syndrome.

Proceeding directly to imaging of the abdomen, pelvis, and chest is often the best option.

9. What procedures are best to localize the source of carcinoid syndrome?

CT imaging of the suspected tumor location (usually starting with the abdomen and pelvis) is the best initial study. MRI is preferred by some because of its superior detection of hepatic metastases. Somatostatin-receptor-based imaging with 68-Ga Dotatate, 68-Ga Dotatoc, and Cu-64 Dotatate, especially when combined with PET/CT, can be particularly useful when a tumor is not detected by cross-sectional imaging.

10. What is the treatment for carcinoid syndrome?

Surgery can be curative when carcinoid syndrome results from a NET that has not metastasized. However, approximately 90% of patients with carcinoid syndrome have extensive metastases at the time of diagnosis. The goal of therapy, therefore, is often to provide palliation and prolong survival.

11. How does one control carcinoid syndrome symptoms?

The most troublesome symptoms of carcinoid syndrome are intense flushing and secretory diarrhea. Long-acting somatostatin analogs (Octreotide, Lanreotide) are the most effective medications for these symptoms because nearly 80% of NETs express somatostatin receptors. Recommended starting doses are Octreotide LAR 20–30 mg every 4 weeks (with dose escalation up to 60 mg every 4 weeks) or Lanreotide 60–120 mg every 4 weeks. Short-acting Octreotide can be used to treat intermittent breakthrough symptoms at doses of 100–500 mcg, as needed, every 8 hours. Positive somatostatin receptor–based imaging predicts a good response to somatostatin analogs, but it has not been established that positive imaging is necessary before starting these agents. There is also evidence that somatostatin analogs may have direct effects to inhibit tumor growth.

12. What medications may be effective when somatostatin analogs do not adequately control carcinoid symptoms?

Telotristat is an orally administered inhibitor of tryptophan hydroxylase, the rate-limiting step in serotonin synthesis. Telotristat used in combination with somatostatin analogs significantly reduces both 5 HIAA excretion and diarrhea. It may also be effective in preventing the progression of carcinoid heart disease. Other medications can be added if symptom control is inadequate. Table 62.2 lists various medication options for relief of refractory symptoms.

13. Are chemotherapy regimens effective for the treatment of NETs?

Cytotoxic chemotherapy has produced disappointing results in carcinoid syndrome. Etoposide plus Cisplatin is the most commonly used regimen for poorly differentiated NETs. Everolimus,

TABLE 62.2 Medications for Relief of Symptoms Related to Carcinoid Syndrome

MEDICATIONS TO CONTROL CARCINOID FLUSHING	
Octreotide (Sandostatin)	50–150 mcg two or three times/day subcutaneously
Octreotide, Long Acting (Sandostatin LAR)	20–30 mg every month intragluteally
Lanreotide (Somatuline)	60–120 mg every month subcutaneously
Phentolamine (Regitine)	25–50 mg 1–3 times/day
Phenoxybenzamine (Dibenzyline)	30 mg/day
Cyproheptadine (Periactin)	2–4 mg 3 or 4 times/day
Methysergide (Sansert)	2 mg 3 times/day
Prochlorperazine (Compazine)	5–10 mg every 4–6 hours
Chlorpromazine (Thorazine)	10–25 mg every 4–6 hours
Clonidine (Catapres)	0.1–0.2 mg 2 times/day
Methyldopa (Aldomet)	250 mg 3 times/day
Cimetidine (Tagamet), plus	300 mg 3 times/day
Diphenhydramine (Benadryl)	50 mg 4 times/day
Glucocorticoids	
MEDICATIONS TO CONTROL CARCINOID DIARRHEA	
Standard antidiarrheal measures, plus:	
Octreotide (Sandostatin)	50–150 mcg 2 or 3 times/day subcutaneously
Octreotide, Long Acting (Sandostatin LAR)	20–30 mg every month intragluteal
Lanreotide (Somatuline)	60–120 mg every month subcutaneous
Telotristat (Xermelo)	250–500 mg 3 times/day
Clonidine (Catapres)	0.1–0.2 mg 2 times/day
Cyproheptadine (Periactin)	2–4 mg 3 or 4 times/day
Methysergide (Sansert)	2 mg 3 times/day
Ondansetron (Zofran)	8 mg 3 times/day

an antagonist of the mechanistic target of rapamycin (mTOR), and vascular endothelial growth factor receptor (VEGF-R) antagonists, such as vatalanib, sunitinib, sorafenib, and bevazuzimab, are also under investigation. Other agents that have shown limited benefit include streptozotocin, 5-fluorouracil, lomustine, doxorubicin, and dacarbazine.

14. What other treatments may be effective for palliation or prolongation of survival in carcinoid syndrome patients?

Hepatic resection is an option in patients with focal liver metastases. Other approaches include hepatic artery embolization, chemoembolization, 90-Y microsphere radioembolization, and peptide receptor radionuclide therapy (PRRT).

15. What is a peptide receptor radionuclide therapy?

Peptide receptor radionuclide therapy (PRRT) takes advantage of the presence of somatostatin receptors on NETs to deliver radiopharmaceuticals that bind to somatostatin receptors directly in tumors. NETs that show significant uptake on somatostatin receptor–based imaging (68-Ga Dotatate, 68-Ga Dotatoc, and Cu-64 Dotatate) often respond well to the theranostic agent 177Lu-Dotatate (Luthera).

TABLE 62.3 Management of Carcinoid Crisis

MEDICATION	DOSE REGIMEN
Octreotide (Sandostatin)	50 mcg IV × 1 min, then 50 mg IV × 15 min
Hydrocortisone (Solu-Cortef)	100 mg IV × 15 min
Methotrimeprazine (Levoprome)	2.5–5.0 mg slow IV push
Methoxamine (Vasoxyl)	3–5 mg slow IV push, followed by infusion
Phentolamine (Regitine)	5 mg slow IV push
Ondansetron (Zofran)	20 mg IV × 15 min
Glucagon	0.5–1.5 mg slow IV push

IV, intravenous.
From Warner RRP. Gut neuroendocrine tumors. In: Bardin CW, ed. *Current Therapy in Endocrinology and Metabolism*. 6th ed. Mosby; 1997:606–614.

16. What is theranostics?

Theranostics uses diagnostic imaging to identify a molecule of interest in cancer cells with subsequent development of a precision radionuclide therapeutic that targets that molecule. A classic theranostic is radioactive iodine, I-131, which has been used since the 1940s to evaluate and treat thyroid cancer. Somatostatin receptor–based imaging followed by PRRT now has a significant role in the treatment of advanced NETs.

17. What is a carcinoid crisis?

Carcinoid crisis is a life-threatening episode of hypotension, flushing, and bronchospasm that is triggered most often by tumor manipulation or anesthesia and less commonly by chemotherapy, hepatic artery embolization, or radionuclide therapy. It can also be provoked by the administration of adrenergic agents, such as epinephrine and sympathomimetic amines, or monoamine oxidase (MAO) inhibitors in people with underlying NETs.

18. How can a carcinoid crisis be prevented?

When people with NETs undergo surgery or hepatic artery embolization, they should be pretreated with octreotide 300–500 mcg SQ or IV 30–60 minutes before the procedure. Repeat dosing during the procedure may be needed to prevent hypotension. Despite these measures, the carcinoid crisis can still occur. Anesthesiologists should be specifically notified that a patient has carcinoid syndrome. Epinephrine, sympathomimetic amines, and MAO inhibitors should be avoided in patients with carcinoid syndrome.

19. Which patients should receive prophylaxis to prevent a carcinoid crisis?

All patients with symptomatic carcinoid syndrome, even if symptoms are well controlled, should receive octreotide prophylaxis for surgery or procedures that can precipitate a carcinoid crisis. Patients who have metastatic NETs, even in the absence of carcinoid syndrome, should have a measurement of 24-hour urine 5 HIAA excretion; octreotide prophylaxis should be used in those with elevated 5 HIAA levels.

20. Describe the management of a carcinoid crisis.

Carcinoid crisis is treated with IV octreotide and steroids. If this does not abort the episode, additional options include methotrimeprazine (antiserotonin agent), methoxamine (direct vasoconstrictor), phentolamine (alpha-adrenergic blocker), ondansetron (serotonin receptor antagonist), and glucagon. It is critical to avoid adrenergic and sympathomimetic agents in patients with suspected carcinoid crisis because these drugs can significantly worsen the condition. Effective medication dose regimens are listed in Table 62.3.

KEY POINTS

Carcinoid Syndrome

- Carcinoid syndrome results from metastatic NETs that produce multiple humoral mediators that cause flushing, diarrhea, bronchospasm, and fibrosis of the endocardium, heart valves, pleura, peritoneum, and retroperitoneal spaces.
- Most patients with carcinoid syndrome have extensive liver metastases that impair the metabolic clearance of mediators secreted by the primary tumor or that secrete the mediators directly into the systemic circulation via the hepatic vein.
- Carcinoid syndrome is usually diagnosed by demonstrating markedly increased urine excretion of 5-HIAA.
- Cross-sectional imaging with CT or MRI is the best way to localize NETs that cause carcinoid syndrome; somatostatin receptor–based imaging combined with PET/CT is useful when tumors cannot be localized with CT or MRI.
- The treatment for carcinoid syndrome is surgical removal of the primary tumor, when possible, or palliation of symptoms by giving medications that reduce the secretion of the humoral mediators or antagonize their effects.
- Carcinoid crisis can be precipitated when a patient with carcinoid syndrome or a secreting NET has a procedure or manipulation of the NET or is given an adrenergic or sympathomimetic medication or a MAO inhibitor.
- Carcinoid crisis is best treated with IV octreotide and hydrocortisone and avoidance of adrenergic and sympathomimetic agents for hypotension.

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CHAPTER 63

Aging and Endocrinology

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1. What effect does aging have on body weight?

Aging–associated body weight changes are complex, not uniform, and likely influenced by changes in the hormonal milieu. In general, body weight increases with age until about age 60 years, after which it decreases (related to the disproportionate decrease in muscle mass). The reduction in body weight in older adults, whether intentional or unintentional, has been associated with an "anorexia of aging" related, in part, to changes in energy intake and appetite–related hormones. Weight loss in older adults also appears to be associated with an increase in mortality (all-cause and cause-specific mortality, including cancer- and cardiovascular disease-specific mortality), morbidity, and disability.

On the other hand, there is a well-described obesity paradox in older adults where higher body mass index (BMI) is associated with lower overall mortality. The causes for this paradox remain unclear and deserve further study. More research is needed on which body composition metrics are most predictive of health outcomes in older adults with different BMIs. Weight loss in the face of illness or diseases of older age that raise cytokine levels may predispose to a disproportionate loss of weight as lean mass (i.e., muscle mass), thereby exacerbating sarcopenia (i.e., age–related loss of muscle mass and strength) and leading to a catabolic state. It is also possible that the onset of obesity at different ages leads to differential outcomes, with obesity beginning at young or middle age being associated with untoward metabolic consequences and obesity beginning at older age being less dangerous to health. Interventions in these two potentially heterogeneous groups might also be expected to produce different health–related outcomes but these have not been studied.

2. What changes in lean body mass occur with aging?

There is an inevitable loss of lean body mass, mostly skeletal muscle, with aging (see Table 63.1). Cross-sectional studies demonstrate that starting at age 30 years, 1–2% of muscle is lost per year, and by age 80 years, a 20–30% loss of lean mass from baseline is observed. The mechanisms underlying the loss of muscle mass with aging include declines in sex hormones, myocyte apoptosis, and mitochondrial dysfunction. Secondary causes of sarcopenia include disuse due to immobility and sedentary lifestyle, inadequate nutrition, and impacts from endocrine and inflammatory diseases. The age–related loss of muscle mass has been blamed for much, but not all, of the age–related decline in muscle strength and power. Longitudinal studies have shown that the decline in strength outpaces the loss of lean mass, with up to a 60% loss in strength from age 30–80 years. Furthermore, the loss of strength and power is not as linear as the loss of muscle mass and seems to accelerate at older ages. A 25% decline in strength has been detected between 70 and 75 years of age. Power (work per unit time) may decline at double the rate of strength. These changes in lean mass, muscle mass, strength, and power have complex but important functional consequences for older adults. Of greatest clinical importance are the relationships between muscle mass, strength or power, and functional ability. These relationships are complex and probably nonlinear, and in general have been hard to demonstrate clearly. An example is the consistent association of testosterone supplementation with increases in lean mass but inconsistent associations with improvements in strength or function.

The term *sarcopenic obesity* refers to the age–associated loss of muscle mass and/or muscle function (i.e., strength) coupled with increased adiposity. Consensus on diagnostic tools or definition of sarcopenic obesity is lacking, and therefore prevalence, clinical relevance, and optimal treatment have not been fully established. Prospective studies show older men with sarcopenia and obesity have the highest risk of all-cause mortality even after adjustment for lifestyle factors (e.g., smoking, alcohol intake, physical activity, and occupation), cardiovascular disease, inflammation, and weight loss. These data support the importance of implementing weight loss programs in older adults that maintain lean mass. One contributing factor to developing sarcopenic obesity

TABLE 63.1 Body Composition Changes With Aging

	CHANGE
Fat Mass	↑
Lean Mass	↓
Muscle Mass	↓
Bone Mass	↓

↑, Increased; ↓, decreased.

could be weight cycling with loss of lean and fat mass followed by regain of fat mass only. This might be more likely in older adults who are less anabolic and generally less active. The loss of lean mass with aging can have a profound effect on resting metabolic rate and thus predispose to further accretion of fat mass if caloric intake is not reduced.

3. Does fat mass increase and/or get redistributed with aging?

The loss of lean mass with aging is accompanied by an increase in fat mass (see Table 63.1). Specifically, there is an increase in total adiposity and a shift in fat from lower body subcutaneous toward more abdominal visceral fat depots with advancing age. An increase in central adiposity begins in young men who gain excess fat, but this does not appear to occur in women until around the time of the menopausal transition. Aging is also associated with an increase in fat deposition in ectopic depots including cardiac and skeletal muscle tissues. Although the loss of lean mass was once thought to be the primary determinant of physical disability in old age, recent studies indicate that increased adiposity is an independent, and perhaps stronger predictor of disability in older individuals. The infiltration of fat into skeletal muscle is associated with reduced lower leg strength and power and impaired physical function. Combined with an increase in visceral adiposity, this may play a role in age–associated insulin resistance.

4. Does menopause trigger an increase in abdominal adiposity in women?

Evidence supports that the menopause transition is associated with adverse changes in body composition, including an increase in fat mass, particularly in the abdominal region. Cross-sectional comparisons of women categorized according to stages of reproductive aging show greater waist size across menopausal stages. Prospective cohort studies indicate an increase in total fat mass and a disproportionate increase in abdominal fat that are related to both chronologic and ovarian age, with the most rapid increases in abdominal fat occurring in perimenopausal women. Furthermore, abdominal subcutaneous and visceral fat increased with the menopause transition without significant changes in body weight or lean mass after adjusting for age. Women who had an oophorectomy before the age of 40 years had greater waist size compared to women who did not have an oophorectomy. The increase in fat mass and abdominal adiposity with menopause is related, in part, to the decline in estradiol. Studies treating premenopausal women with gonadotropin-releasing hormone agonists to suppress sex hormones show fat mass gains of 1–2 kg in 4–6 months, with a disproportionate increase in central body fat, and this is prevented by the administration of estradiol. Finally, several randomized controlled trials have shown that postmenopausal women treated with estrogens with or without progestins gain less weight and have less increase in waist size than placebo-treated women. The effects seem to be slightly larger with unopposed estrogens. Recent studies in animals suggest a possible role for the increase in FSH with the menopause transition as a mechanism for the increase in adiposity. Animals treated with an FSH antibody had a marked reduction in adiposity that was more pronounced in the abdominal visceral region. It has not yet been determined whether estrogens and/or blocking the increase in FSH specifically prevent or attenuate intraabdominal fat accumulation.

5. What are the results of prospective studies of weight loss through lifestyle, weight loss medications, or weight loss surgery in older adults?

Obesity in older adults is a mounting public health concern given its increasing incidence and association with loss of functional independence and frailty. Hypocaloric diets have been effective in reducing total and visceral fat and improving glucose tolerance, insulin sensitivity, blood pressure, and pulmonary function. Older adults with obesity can participate and adhere to rigorous interventions such as diet, exercise, and diet plus exercise. Such studies have found that diet alone and exercise alone both reduce frailty, but the combination of diet and exercise generates the greatest objective functional and subjective benefits.

Intentional weight loss typically results in a loss of lean mass (muscle and bone), which may exacerbate sarcopenia and risk for osteoporosis. This could have adverse effects in older adults who are already at risk for osteoporosis. Thus, it is recommended that exercise training should be added to diet interventions to mitigate the loss of lean mass. Using this approach, the addition of exercise training to diet in older adults with obesity prevented the weight loss–induced increase in bone turnover and attenuated, but did not prevent, the decline in bone mineral density (BMD). A systemic review and meta-analysis also revealed that protein intake higher than the recommended dietary allowance was cross-sectionally associated with better physical performance and greater muscle strength in older adults compared to diets with lower protein intake, though longitudinal studies did not show that higher-protein diets prevented a decline in physical function.

Some prospective observational studies have suggested that weight loss in older adults may be associated with increased mortality, despite a decrease in comorbidities such as cardiovascular diseases (CVD) and type 2 diabetes mellitus. However, in randomized controlled weight loss interventions, weight loss did not increase mortality in older adults over 8–12 years of follow-up. In fact, secondary analyses from one trial suggested that intentional weight loss might reduce mortality risk in this population. Additional trials of intentional weight loss in older adults are needed to confirm whether it does indeed reduce mortality risk and whether the risk-to-benefit profile is similar in older adults who develop obesity earlier versus later in life.

Data are lacking regarding the efficacy and safety of current FDA-approved antiobesity pharmacotherapy in older adults because trials had low percentages of older adults, who may have been excluded due to age–related comorbidities. Age–related outcomes (e.g., body composition, muscle function, and BMD have also not been evaluated in the trials where weight loss was the primary outcome. Trials for orlistat, a lipase inhibitor, had very few adults aged ≥65 years; therefore, it is difficult to determine body weight differences by age group, though side effect profiles appear to be similar. Naltrexone/bupropion, the opioid antagonist/dopamine-norepinephrine reuptake inhibitor, was examined in the COR-I trial, but with only 2% of adults aged ≥65 years and none aged ≥75 years, differential outcomes by age group are unknown. Trials for the glucagon-like peptide 1 (GLP1) receptor agonists, liraglutide and semaglutide, included 5–7% to 9–20% of adults aged ≥65 years, respectively. Conclusions have been mixed, such as (1) no difference in GLP1 receptor agonist safety/efficacy between younger and older adults or (2) increasing age being associated with more adverse effects from GLP1 receptor agonists. Lastly, the SURMOUNT-1 trial for tirzepatide, the dual GLP1/gastric inhibitory polypeptide receptor agonist, included 6% of participants aged ≥65 years, but there were no data on outcomes by age group.

Weight loss surgery is effective at reducing weight and medical comorbidities in older adults, though at higher perioperative risk. A recent systematic review of 26 studies of 8149 adults aged ≥60 years revealed a pooled 30-day postoperative mortality rate of 0.01% and an overall complication rate of approximately 15%. After 1 year, pooled mean excess weight loss was 54%, and the resolution of diabetes, hypertension, and lipid disorders was 55%, 43%, and 41%, respectively. These improvements are comparable to those seen in younger adults and appear to be independent of bariatric surgery procedure. There also does not appear to be an increased mortality in older adults who underwent Roux-en-Y gastric bypass compared to nonsurgical older controls.

6. What changes in bone health occur with aging?

Prospective data indicate that peak bone mass occurs during the late teenage years to the early 20s. Because of the intimate structural and functional link between muscle and bone, the occurrence of peak bone mass likely corresponds with peak skeletal muscle development. It is generally thought that bone mass is maintained, or decreases slowly (<0.2% per year), through approximately age 50. Intuitively, a decline in physical activity during middle age might be expected to induce an even faster rate of bone loss. However, the increase in body weight that typically also occurs during middle age may somewhat counter this by increasing mechanical loading forces acting on the skeleton during weight-bearing activity. There is an inevitable loss of bone mass in older adulthood (see Table 63.1) that increases the risk for osteoporosis in older men and can exacerbate the risk for osteoporosis in postmenopausal women. In older women and men, the decrease in BMD at the hip appears to be accelerated (approximately 1% per year) relative to the changes at the spine, which may increase in advanced age. Vertebral compression fractures and the development of extravertebral osteophytes lead to an increase in BMD that does not reflect increased vertebral bone strength. The utility of spine BMD for the diagnosis of osteoporosis in older adults is therefore diminished.

In addition to bone density, bone quality is also a component of overall bone strength; changes in bone quality can increase the risk for osteoporotic fracture. Bone quality properties include porosity, architecture and geometry, turnover, damage, and mineral content. Higher-resolution imaging techniques suggest that overall bone quality declines with age through factors such as increased cortical and trabecular porosity and decreased volumetric BMD. These changes are not captured by standard dual-energy x-ray absorptiometry (DXA) screening.

7. Does menopause have an independent effect on bone health?

The decline in BMD accelerates in the late perimenopausal and early postmenopausal periods in women. What remains somewhat controversial is whether the menopause-induced increase in bone resorption diminishes after a few years or persists throughout older adulthood. In this regard, observational studies of women aged 65 years and older indicate that the rate of bone loss continues to increase with age, particularly in the hip region. This is corroborated by observations that serum markers of bone turnover increase at menopause and remain elevated into older age. Recent studies in animals implicate both the decrease in estrogens and the increase in follicle stimulating hormone (FSH) as mechanisms underlying bone loss with the menopausal transition. Inhibition of FSH activity prevented ovariectomy-induced bone loss. However, whether the increase in FSH with menopause contributes to the decline in bone mass in women remains unclear.

8. Can weight-bearing exercise prevent the menopause-related loss of bone mineral in women?

It is unlikely that even vigorous weight-bearing exercise can completely mitigate the deleterious effects of estrogen deficiency on BMD. Older female athletes not on hormone therapy have lower BMD than premenopausal athletes. Additionally, young female athletes with menstrual cycle dysfunction can have impaired BMD (1.0–2.5 SD below the average peak bone mineral density) and even critically low bone mineral density (>2.5 SD below the average peak bone mineral density), despite their participation in sports that involve high levels of mechanical loading (e.g., gymnastics, distance running). Moreover, in premenopausal women undergoing ovarian hormone suppression, concurrent resistance exercise training only mitigated some of the decline in bone mineral density at the proximal femur and did not prevent the decline in bone mineral density at the lumbar spine.

9. Do sex hormones influence the skeletal response to exercise?

In animal models, the effects of mechanical stress in the presence of estrogens (in females) or androgens (in males) on the bone proliferative response have been found to be either additive or synergistic (i.e., more than additive). There is also evidence for additive or synergistic effects of exercise and estrogens on BMD in women. In postmenopausal women, hormone therapy concurrent with exercise training had a greater beneficial effect on hip and spine BMD than exercise alone. There is some evidence that in postmenopausal women treated with hormone therapy, mixed loading exercise protocols such as high-impact weight-bearing activities (e.g., jumping) combined with progressive resistance training may have a greater benefit on BMD than single-mode exercise.

The response of bone cells to mechanical stress involves the activation of estrogen receptor alpha. Recent studies of laboratory animals suggest that estrogen receptor alpha may facilitate the effects of mechanical loading on bone whereas estrogen receptor beta may inhibit such effects. Additionally, the mechanical loading effects facilitated by estrogen receptor alpha signaling may be impaired in postmenopausal women because of reduced estrogens. However, the effects of age–related sex hormone deficiency on receptor density and/or function in bone remain unknown.

10. What criteria are used to determine who should be treated for low bone density?

DXA is the standard means of following changes in BMD in older adults. Clinical practice guidelines recommend bone density screening to identify osteoporosis in all women aged 65 years and older and in men aged 70 years and older. Earlier bone density screening and/or vertebral imaging is recommended for adults at age 50 years with clinical risk factors for fracture (see below). T-scores between -1.0 and +1.0 indicate normal bone density, whereas T-scores between –1.0 and –2.5 indicate low bone mass (also referred to as osteopenia). T-scores less than or equal to –2.5 indicate osteoporosis. Pharmacotherapy for low BMD is not reserved only for those with osteoporosis. The University of Sheffield launched the FRAX® tool in 2008, which can be used to evaluate the fracture risk in individuals aged 40–90 years. The FRAX® algorithm gives an individual's 10-year probability of major osteoporotic and hip fractures and can identify those adults who would benefit from treatment. The FRAX® tool may be used with or without a screening BMD measurement and considers several criteria, including race/ethnicity, age, gender, personal history (and family history) of fracture, current smoking, alcohol use, glucocorticoid use, and having a disorder or chronic disease associated with osteoporosis. For the United States, Food and Drug Administration (FDA)-approved medical therapies should be considered in postmenopausal women and men aged ≥50 years if they have (1) a hip or vertebral (clinical or morphometric) fracture; (2) a T-score ≤-2.5 at the femoral neck or spine (excluding secondary causes); and/or (3) a T-score <-1.0 but >-2.5 at the femoral neck or spine *and* a 10-year probability of ≥20% for a major osteoporosis–related fracture or ≥3% for a hip fracture. Additionally, clinical judgment and/or patient preference should be considered for adults with T-scores or 10-year probabilities outside of these values.

11. What pharmacologic agents are available for use in older adults with low bone density?

In addition to lifestyle recommendations for all adults, including adequate intake of calcium and vitamin D through the diet or supplements, several FDA-approved agents are available for management of low bone mass and osteoporosis in individuals at high risk for fracture. Bisphosphonates, antiresorptive agents that act by inhibiting osteoclast function and enhancing osteoclast apoptosis, are the first-line medications for fracture prevention at all major sites. For adults older than 80 years, risedronate and zoledronic acid are the only bisphosphonates to show significant reductions in new vertebral, hip, and nonvertebral fractures during a 3-year period. Possible side effects of oral bisphosphonate therapies include dysphagia and esophagitis. Oral and intravenous bisphosphonates may impair renal function and are contraindicated in adults with estimated glomerular filtration <30–35 mL/min. There have been reports of rare but serious side effects such as avascular necrosis, osteonecrosis of the jaw, and low-trauma atypical femur fractures (subtrochanteric and diaphyseal femur fractures) associated with longer-term bisphosphonate use (>3–5 years). Recommendations are to periodically reevaluate indications for continued bisphosphonate therapy, particularly in adults who have been treated for over 5 years, and to always ask about symptoms such as new thigh or groin pain.

Commonly prescribed alternatives to oral or intravenous bisphosphonates include anabolic agents (teriparatide, abaloparatide), denosumab, and romosozumab.

The FDA-approved anabolic drugs include teriparatide, which is recombinant human PTH (1-34), and abaloparatide, which has 41% homology to PTH (1-34) and 76% homology to PTHrP (1-34). These agents improve BMD and prevent fractures by stimulating osteoblast function through intermittent interaction with the PTH/PTHrP-1 receptor. They are administered via daily subcutaneous injection, which is important to consider in older adults who may not have the functional capacity or appropriate assistance to do so. Cumulative parathyroid hormone therapy should not exceed 2 years.

Denosumab is a human monoclonal antibody that binds receptor activator of nuclear factor kappa-B ligand (RANKL) to prevent RANKL/RANK interaction, and thereby reduces osteoclast formation and function. As an antiresorptive osteoporosis agent, it has the net effect of increasing BMD in women and men and reducing risk of fracture (better data for fracture reduction in women). Use of denosumab could be considered in adults who have failed or are intolerant of bisphosphonates and in adults for whom bisphosphonates are contraindicated for impaired renal function. No dose adjustment is necessary in adults with renal impairment as denosumab is not renally cleared, although renal patients and those with poor calcium absorption are at higher risk for hypocalcemia. Additionally, because RANKL functions within the immune system, long-term monitoring will be needed to assess the increased risk for serious infections and neoplasms. Denosumab, administered once every 6 months by subcutaneous injection, is dosed continuously without a drug holiday. Subsequent therapy with another agent is necessary because adults are at increased risk for vertebral fracture following discontinuation of denosumab.

The newest osteoporosis medication, romosozumab, is a monoclonal antibody sclerostin inhibitor. Sclerostin is a protein expressed by SOST and reduces osteoblastic bone formation. Romosozumab works by binding to sclerostin and thereby increases osteogenesis. Romosozumab is administered as a monthly injection for 12 months, after which effects have been shown to diminish. Side effects include hypercalcemia, so it should not be used in adults with a history of hypercalcemia, and it is also not recommended for adults with a history of myocardial infarction or stroke in the past year. Currently, romosozumab is only indicated for women after menopause at increased risk for fracture or who did not respond to or tolerate other osteoporosis medications.

12. Why is vitamin D status important in older adults?

Vitamin D supplementation has been found to reduce the incidence of osteoporotic fractures in older adults. This may occur via increased bone mineralization, improved muscle function, reduction in falls, or a combination of these effects. According to the Institute of Medicine, vitamin D deficiency is defined as a 25-hydroxyvitamin D (25[OH]D) level <20 ng/mL (50 nmol/L). National and international groups have suggested that a 25(OH)D level ≥30 ng/mL (75 nmol/L) is needed to minimize fracture and fall risk. There are insufficient data to recommend a safe upper limit of 25(OH)D.

It has been estimated that more than 40% of community-dwelling older women and men in the United States are vitamin D deficient, and the prevalence is even higher in nursing home residents. There are multiple causes of vitamin D deficiency in older adults, including decreased skin synthesis; decreased sun exposure; decreased intake; impaired absorption, transport, or liver hydroxylation of oral vitamin D; medications altering vitamin D metabolism (e.g., drugs that induce P450 enzymatic activity leading to decreased circulating levels of 25[OH] D); chronic illnesses associated with malabsorption; and liver and kidney disease.

BMD decreases when serum 25(OH) D is <30 ng/mL. Vitamin D3 supplementation of 700–800 IU/day or 100,000 IU every 4 months has been found to raise serum 25(OH) D above 30 ng/mL and reduce the incidence of fractures. However, a 2022 umbrella review of meta-analyses of vitamin D randomized controlled clinical trials showed that only combined calcium and vitamin D supplementation and not vitamin D alone reduced the risk of fracture. There is currently no evidence supporting D2 supplementation for fracture prevention.

Vitamin D deficiency also causes muscle weakness. Proximal muscle strength is linearly related with serum 25(OH)D when levels are less than 30 ng/mL. Vitamin D supplementation has been associated with a 22% reduction in falls. Nursing home residents randomized to receive 800 IU/day of vitamin D2 plus calcium had a 72% reduction in falls.

In addition to its important role in muscle and bone metabolism, vitamin D deficiency has been shown to increase the risk of ischemic heart disease, myocardial infarction, and ischemic stroke. An inverse relationship between 25(OH)D levels and colorectal—but not breast and prostate—cancer has been reported. With respect to cognition, a meta-analysis of 26 observational studies of adults aged 65 years or older identified that low 25(OH)D was associated with lower cognitive function. Epidemiological studies also demonstrate higher mortality in adults with insufficient or deficient levels of 25(OH)D.

13. What are the recommendations for vitamin D supplementation in older adults?

The 2010 Institute of Medicine recommendations for vitamin D supplementation are set at 600 IU/day for men and women aged 51–70 years and 800 IU/day for older individuals.

In 2010, the National Osteoporosis Foundation (NOF) recommended that older adults should have a serum 25(OH)D level of 30 ng/mL (75 nmol/L) to reduce the risk for falls and fractures. Supplementation doses up to 800–1000 IU/day were recommended because of the lack of evidence for the efficacy of higher doses.

The 2011 Endocrine Society clinical practice guidelines suggested maintaining a serum 25(OH)D of 30 ng/mL (75 nmol/L) with vitamin D2 or D3 1500–2000 IU/day.

In 2012, the United States Preventive Services Task Force (USPSTF) reported that supplementation of 400 IU/day vitamin D in combination with 1000 mg/day calcium does not reduce fracture risk in non-institutionalized, community-dwelling, asymptomatic adults without a previous history of fractures. In 2018, the USPSTF recommended against daily supplementation with 400 IU vitamin D in combination with 1000 mg calcium for primary fracture prevention of community-dwelling postmenopausal women but cited insufficient evidence to make a recommendation for men and premenopausal women. The USPSTF noted a lack of evidence regarding the effectiveness of higher doses of vitamin D and calcium on primary fracture prevention for community dwelling postmenopausal women.

14. What interventions have been associated with increased longevity, and have they been shown to work in humans?

Animal studies have demonstrated that generating negative energy balance in rodents through increased energy expenditure (exercise) results in improvements in mean life span (average life expectancy) but does not increase the maximal life span. In humans, a meta-analysis of 15 studies on the association of daily steps and all-cause mortality reported a progressive decrease in risk of mortality among adults aged 60 years and older with increasing number of daily steps until 6000–8000 steps/day.

Caloric restriction (30–40% reduction in daily energy intake) increases mean life span (average life expectancy) and maximal life span in yeast, worms, flies, rodents, and mammals. Studies in humans suggest that 10–30% caloric restriction produces physiologic, metabolic, and hormonal effects that parallel many of the positive effects found in other species. Caloric restriction intervention trials with durations of 6 months to 2 years in healthy adults found that caloric restriction led to improvements in cardiometabolic risk and did not adversely affect quality of life. Physical and psychological adverse effects have been observed with overprescription of caloric restriction, and adequate macro- and micronutrient intake based on recommended daily allowance is recommended.

Studies have reported that dietary composition also plays a role in longevity. A large meta-analysis of data from the Consortium on Health and Ageing: Network of Cohorts in Europe and the United States (CHANCES), including 400,000 older adults, found adherence to a healthy diet (limited intake of saturated fatty acids, monosaccharides, disaccharides, and cholesterol; 6–10% of energy intake from polyunsaturated fatty acids [PUFAs] and 10–15% from protein; and adequate fruit and vegetable intake of >25 g/day of fiber and >400 g/day of fruits and vegetables) was associated with increased life expectancy. Though prolonged dietary intervention trials for longevity typically study biomarkers of longevity rather than life span, the majority of evidence shows prolonged adherence to similar diets (e.g., Mediterranean) with or without caloric restriction have led to improved indices of insulin sensitivity, oxidative stress, and other cardiovascular risk factors. A 5-year primary prevention trial in older adults at high CVD risk showed consumption of Mediterranean-style diets led to a decrease in incident CVD, type 2 diabetes, peripheral artery disease, and atrial fibrillation in men and women.

No medications or supplements have been shown to increase longevity in randomized controlled clinical trials. One study showed an association (but not causation) with decreased mortality in adults with diabetes using metformin compared to matched adults without diabetes not using metformin. The Targeting Aging with Metformin (TAME) Trial aims to investigate the effect of metformin in the development of heart disease, cancer, and dementia in people between the ages of 65–79 years.

15. What happens to testosterone and estradiol levels with aging in men?

Serum total testosterone represents the unbound and protein-bound testosterone in circulation. Most testosterone is bound to sex hormone binding globulin (SHBG) and albumin; only 2–4% of circulating testosterone is unbound or free. In general, serum total testosterone declines gradually at an average of 1.6% per year with advancing age (see Table 63.2). Additionally, SHBG levels increase with age, resulting in an even greater relative reduction in calculated bioavailable and free testosterone with age (declines of 2–3% per year).

The decline in testosterone with aging in men is variable and reference ranges across age groups are wide. Samples from four large cohort studies of men without obesity from Europe and the United States were used to measure testosterone concentrations with a reference method

TABLE 63.2 Hormone Changes With Aging

	WOMEN	MEN
Estradiol	↓	↓
Testosterone	↓	↓
Growth Hormone	↓	↓
IGF1	↓	↓
DHEAS	↓	↓
TSH	↑	↑
Cortisol	↑	↑

↑, Increased; ↓, decreased; *IGF1,* insulin-like growth factor 1; *DHEAS,* dehydroepiandrosterone sulfate; *TSH,* thyroid stimulating hormone.

at the Centers for Disease Control and Prevention. The authors modeled estimates for 2.5th and 97.5th percentile testosterone concentrations for men ages 19–39, 40–49, 50–59, 60–69, 70–79, and 80–99 years. The 2.5th to 97.5th percentile testosterone concentration range for men aged 19–39 years was 267–929 ng/dL, while the 2.5th to 97.5th percentile for men aged 80–99 years was 157–913 ng/dL.

Although testosterone is converted to estradiol via aromatase, total serum estradiol levels in adult men do not change significantly with age. In fact, serum estradiol levels of older males maybe two- to fourfold higher than in postmenopausal women of the same age. However, bioavailable and free estradiol levels decrease due to the increase in SHBG with aging (estradiol binds to SHBG with half the affinity of testosterone).

16. What is the cause of decreases in male testosterone levels with aging?

Changes in health and lifestyle factors contribute to the variability of testosterone concentrations. For example, obesity and comorbid diseases, including diabetes, are associated with greater rates of decline in testosterone. In a prospective cohort study of men aged 40–70 years at baseline, total testosterone was approximately 12% lower in men with BMIs in the obesity range compared to men without obesity. This was comparable to the approximately 13% decline in total testosterone associated with 10 years of aging when BMI remained stable. Acute and chronic illness, some medications (e.g., narcotics, glucocorticoids), nutritional deficiency, sleep disorders (e.g., obstructive sleep apnea), stress, and widowhood can also reduce testosterone concentrations.

17. What is the prevalence of hypogonadism in older men?

The prevalence of male hypogonadism is not completely known because of the lack of consensus on the definition of hypogonadism with aging and because symptoms of hypogonadism are often nonspecific and can be associated with other chronic conditions. When using a biochemical hypogonadism definition of total testosterone concentrations <325 ng/dL, the Baltimore Longitudinal Study of Aging reported increased prevalence rates of hypogonadism with advancing age with 12%, 19%, 28%, and 49% of men in their 50s, 60s, 70s, and 80s, respectively. However, the prevalence of symptomatic hypogonadism in this study was not reported. When hypogonadism was defined as total testosterone <300 ng/dL and free testosterone <5 ng/dL, almost 50% of men aged 50+ years with hypogonadism were asymptomatic, and 65% of men with symptoms had normal testosterone levels. The prevalence of symptomatic androgen deficiency is estimated to be at least 5% in men aged 50–70 years and 18% in older men.

In 2018, the Endocrine Society published updated testosterone therapy guidelines and recommended that hypogonadism be diagnosed in men with signs and symptoms (e.g., low libido, loss of body hair, hot flushes, decreased energy) of testosterone deficiency and unequivocally and consistently low serum morning testosterone concentrations. Additionally, it is important to confirm low testosterone concentrations because of large day-to-day variability in serum concentrations. Indeed, 30% of men with an initial testosterone value in the hypogonadal range have a normal testosterone value on repeat measures. Serum testosterone has diurnal variation and can be influenced by food and exercise; thus, serum measures should occur in the morning after an overnight fast and abstinence from exercise.

18. Are there benefits of testosterone supplementation for older men with low testosterone levels?

Of the randomized controlled trials in healthy older men with low testosterone levels, most found an increase or maintenance of fat-free mass (bone and muscle) and a decrease in abdominal visceral fat mass with testosterone therapy. Studies have shown that androgen replacement either increased or did not change appendicular intermuscular adipose tissue, so the effects of testosterone on this area of body composition remain uncertain. Whether such physiologic effects translate into strength or functional improvements remains equivocal. Anemia due to androgen insufficiency improves with testosterone therapy, whereas improvements in sexual function and sense of well-being have been inconsistent.

The lack of consistent findings among testosterone supplementation trials is likely related to variability in study cohorts (e.g., baseline testosterone levels, symptoms, body composition, comorbidities, physical function), the type and dose of testosterone therapy (e.g., oral, transdermal, intramuscular), average testosterone levels achieved, and duration of treatment (e.g., months versus years). A placebo-controlled randomized trial of testosterone gel (1%) applied daily for 3 years in 308 older men (age ≥60) that included men with low-normal testosterone levels showed no improvement in insulin sensitivity, atherosclerosis progression, sexual function, or health-related quality of life. These results differ from those of the testosterone trials (seven coordinated placebo-controlled trials) in 788 older men with low testosterone levels that showed normalization of testosterone levels in older men with low testosterone led to improved sexual and physical function, mood, and BMD.

19. Is there evidence for adverse effects of testosterone supplementation in men with low testosterone levels?

Common adverse events reported with testosterone therapy include acne, oily skin, and breast tenderness. There have been reports of small decreases in high-density lipoprotein (HDL) cholesterol with testosterone therapy. Additional adverse effects include worsening of BPH and erythrocytosis; these effects are likely dose related. The effect on erythrocytosis is increased in the presence of sleep apnea and is more pronounced in older men. There is a consistent lack of evidence of increased prostate cancer risk in studies of men on testosterone therapy. Although there is evidence of an association with testosterone administration and increased risk of detecting subclinical prostate cancer in older men, this is likely due to increased surveillance and testosterone-induced rises in prostate-specific antigen (PSA) levels that may lead to increased risk of prostate biopsy. Testosterone use is not recommended in adults with active, untreated prostate cancer; the use of testosterone after treatment of prostate cancer is controversial.

Although observational studies consistently reported an association between low testosterone and increased cardiovascular risk and mortality, the Testosterone in Older Men with Mobility Limitations (TOM) trial and Testosterone Trials studies suggested possible cardiovascular harm in older men receiving testosterone therapy. The participants of the TOM trial were men aged ≥65 years with limitations in mobility and a high prevalence of chronic disease (e.g., diabetes, HTN, obesity), who were randomized to receive testosterone or placebo. During the 6-month intervention, men who were randomized to testosterone gel therapy with a goal total testosterone concentration above 500 ng/dL unexpectedly had a higher prevalence of cardiovascular, respiratory, and dermatologic adverse events after adjustment for baseline risk factors. The increased frequency of cardiovascular events led to trial termination. The Testosterone Trials, in a population that was not as limited in mobility but with a high prevalence of chronic disease, showed an increase in noncalcified coronary plaque size in adults who received testosterone. These findings prompted the Food and Drug Administration to mandate a post-marketing study on the effects of testosterone on cardiovascular risk. The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial enrolled 5246 men (ages 45–80 years) with preexisting cardiovascular disease or elevated cardiovascular risk and at least one symptom of hypogonadism and a fasted morning total testosterone less than 300 ng/dL. The men were randomized to receive 1.62% transdermal testosterone gel or placebo. At a mean treatment duration of 21.7 months, the primary cardiovascular end-point event occurred in 182 men (7.0%) in the testosterone group and 190 men (7.3%) in the placebo group (hazard ratio, 0.96; $P < .001$ for noninferiority). These findings led the authors to conclude that in men with hypogonadism and high risk of cardiovascular disease, transdermal testosterone was noninferior to placebo with respect to incident cardiovascular events. Based on the TRAVERSE trial results, the FDA removed the Boxed Warning language related to adverse cardiovascular outcomes from all testosterone products.

20. What are the recommendations for testosterone replacement therapy in older men with androgen deficiency?

The most recent guidelines from the Endocrine Society published in 2018 recommend against routinely prescribing testosterone to all men aged 65 years and older with low testosterone concentrations. The Endocrine Society recommends screening for and diagnosing androgen deficiency in older men who have signs and symptoms consistent with hypogonadism. They recommend the use of a high-quality assay to measure morning fasting total testosterone concentrations and confirming a low result with a repeat measurement and with a free or bioavailable testosterone concentration if SHBG may be altered or if total testosterone is borderline. If low testosterone concentrations are confirmed, only men with clinically significant and symptomatic androgen deficiency and no contraindications (i.e., planning fertility, presence of a urinary tract or prostate condition, elevated hematocrit or thrombophilia, untreated obstructive sleep apnea, or recent neuro- or cardiovascular event) should be considered for treatment. Men with low testosterone levels should be evaluated for the cause of androgen deficiency. If therapy is initiated, the clinician should ensure that the patient understands the uncertainty of the risks and benefits of testosterone therapy. The choice of supplementation should be at the discretion of both the clinician and patient. Although the Endocrine Society advises a target total testosterone level in the mid–normal range when prescribing testosterone therapy, many clinicians aim for total testosterone levels in the low–normal range to avoid potential cardiovascular or respiratory side effects, despite a lack of evidence supporting this practice. Monitoring patients during the first year of therapy should include evaluations for hematocrit and prostate cancer risk.

21. Should estrogen-based hormone therapy be given to postmenopausal women?

Estrogen-based hormone therapy has been an area of controversy since the completion of the Women's Health Initiative (WHI) trials 20 years ago. Similar to debates about testosterone supplementation, controversy exists regarding who should be treated (e.g., age, years menopausal, symptomatic), by what formulation (e.g., conjugated estrogens versus estradiol, progesterone versus medroxyprogesterone acetate [MPA], continuous versus intermittent progestins), at what dose (e.g., fixed versus targeted serum estradiol level), by what route (i.e., oral, transdermal, transvaginal), and for what length of time. The WHI trials generated important results but raised equally important questions. The risks of oral conjugated estrogens with or without MPA differ, with a more favorable risk profile for estrogen alone. The WHI trials appear to support the "timing hypothesis" that cardiovascular benefits may occur when therapy is initiated near the time of menopause. However, initiating hormone treatment after 10 or more years of estrogen deficiency may increase the risk for cardiovascular events.

The loss of estrogen with menopause (see Table 63.2) appears to be linked with deleterious changes in body composition, including increased central fat accumulation and decreased BMD, which translates long term into increased risk for cardiovascular disease and fractures. Additionally, the loss of estrogen is associated with hot flashes, decreased sleep quality, vaginal dryness, and worsening of mood disturbances, the sum of which equals a decreased quality of life for many women.

As summarized in the North American Menopause Society (NAMS) 2022 hormone therapy position statement, hormone therapy is approved by the FDA as a first-line treatment for the relief of menopausal symptoms including moderate to severe vasomotor and genitourinary symptoms such as vulvovaginal atrophy and dyspareunia. However, the FDA recommends that low-dose topical vaginal estrogen therapy be used for menopause–related genitourinary symptoms in the absence of indications for systemic estrogen therapy. Hormone therapy has also been indicated by the FDA for the prevention, but not treatment, of postmenopausal osteoporosis and hypoestrogenism resulting from hypogonadism, bilateral oophorectomy, or primary ovarian insufficiency. The risks of hormone therapy differ depending on type, dose, route of administration, duration of use, timing of initiation, and whether a progestin is used. For example, transdermal estradiol appears to be associated with fewer thromboembolic events than oral estrogens. Because use of continuous conjugated estrogens plus MPA was associated with increased incidence of invasive breast cancer in the WHI (whereas use of conjugated estrogens alone was not), intermittent progesterone may be a better alternative for endometrial protection. Risk stratification by age and time since the final menstrual period is recommended. The NAMS recommended that hormone therapy be individualized to determine the most appropriate treatment type and duration of use to maximize benefits and minimize risks, with periodic reevaluation to determine an individual woman's benefits and risks of continuing or stopping hormone therapy. Because estrogen therapy alone has a more favorable safety profile, longer duration of treatment may be more appropriate. Discontinuation of systemic hormone therapy in women aged 65 years and older for safety reasons is not supported by evidence. Decisions to continue to use HT in older women should be judged on an individual basis for quality of life, persistent VMS, and/or prevention of bone loss and fractures, with appropriate evaluation of risks. Ultimately, whether to use hormone therapy or not should be incorporated into lifestyle modifications to manage menopausal symptoms and risks for age–associated chronic diseases.

22. How do the concentrations of DHEA and its sulfate DHEAS change with aging?

Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone in humans; approximately 95% comes from the adrenal glands and smaller amounts from the gonads. DHEA is converted to DHEA sulfate (DHEAS) in the adrenal glands and liver. DHEAS is the predominate circulating form of DHEA and is thought to be one of the best biologic markers of human aging. DHEAS concentrations are higher in men than women. Peak serum DHEAS levels are achieved around age 25 years and then decline steadily with advancing age (see Table 63.2). By age 70 years, circulating DHEAS levels are only about 20% of peak levels, and by age 80 years DHEAS levels are similar to childhood concentrations, reflecting the decrease in size of the zona reticularis. The decrease in DHEA with aging does not represent a general decline in adrenal function, as similar changes in other adrenal hormones do not occur.

23. What are the biologic effects of DHEA?

Actions of DHEA are thought to be mediated primarily through conversion to androgen and/or estrogen, and thus it may function as a large storage pool of pre-hormone. DHEA is the precursor for 30–50% of androgens in older men and >70% of androgens in older women and is a major source of estrogens in men and postmenopausal women. Tissues that can be targeted by DHEA include muscle, bone, adipose, blood vessels, cardiac and liver. As such, the decline in DHEA with aging may contribute to physiologic changes that occur because of sex hormone deficiency (e.g., the loss of bone and muscle mass). Other biologic effects of a decline in DHEA with aging may include decreased IGF1 as well as decreased anti-glucocorticoid and antiinflammatory effects via peroxisome proliferator-activated receptor α agonism.

24. What are the hormonal effects of DHEA supplementation?

In the United States, DHEA (called prasterone) is FDA approved as an intravaginal insert to treat symptoms of vulvovaginal atrophy in postmenopausal women. As an over-the-counter product, DHEA is considered a dietary supplement and is therefore not FDA regulated in that setting. Over-the-counter products vary greatly in the amounts of bioactive hormones they contain (if any) and may have quite different pharmacokinetic profiles. Even lot-to-lot variability within a brand can be large. Despite being labeled a "dietary supplement," DHEA has measurable effects on hormone concentrations. In older adults, DHEA 50 mg of bioactive hormone per day results in a 300–600% increase in plasma DHEAS concentrations in men and women; a 100% increase in plasma testosterone in women with nonsignificant changes in men; a 70–300% rise in plasma estradiol in women and 30–200% increase in men; and increases in IGF1 of 25–30% in women and 5–10% in men. However, the physiological effects of DHEA supplementation in humans appear quite variable.

25. Summarize the controlled studies of DHEA administration to older adults

In recent randomized, placebo-controlled trials of 1–2 years, DHEA supplementation (25–50 mg/day) alone in older men and postmenopausal women resulted in DHEAS concentrations within young adult ranges but did not result in significant changes in fat or muscle mass, lipid profile, glucose, mood, or cognitive performance. Shorter studies of DHEA combined with an exercise stimulus (e.g., endurance, resistance, or both) have shown mixed effects. In postmenopausal women, 12 weeks of DHEA was not more effective than placebo at potentiating effects of endurance and resistance exercise on body composition, glucose, or lipid metabolism. In contrast, 16 weeks of DHEA improved muscle volume and strength compared to placebo when combined with high-intensity resistance exercise in older women and men.

Randomized controlled trials on the effects of 1–2 years of DHEA (dosed 50 mg/day) on BMD in older adults have shown trends for increases at the hip, but improvements at other sites appear to be more study and sexspecific. The increases in BMD in response to short-term DHEA therapy have generally been small (1–2%). One study on the effects of DHEA or placebo combined with vitamin D and calcium found that, compared to placebo, spine BMD improved by 1.7% after 1 year in DHEA-treated older women, but it had no effect on BMD in the hip or any site in older men. Further improvements that were equivalent to those seen with bisphosphonate treatment (up to 3.6%) in spine BMD were observed in older women treated with DHEA after 2 years. There have been no randomized controlled trials assessing the effect of DHEA supplementation on fracture risk, but higher endogenous DHEAS is associated with higher lumbar spine BMD and decreases in forearm fracture risk among women of European ancestry with mean ages between 50–74 years.

In general, DHEA replacement trials have not shown significant adverse events (such as increases in PSA in older men), but much larger trials would be needed to establish the safety and efficacy among older men and women. The most common reported adverse effects have been dermatological or androgenic symptoms in postmenopausal women.

26. Describe the changes in the Growth Hormone (GH)/Insulin-Like Growth Factor (IGF)1 axis with aging.

Aging is associated with a significant decline in the GH area under the curve (AUC), as well as the number and amplitude of night-time GH peaks. These changes in GH secretion (approximately 15% decline for every decade after age 30 years) are also associated with a steady decline in IGF1 (see Table 63.2). By age 65 years, most individuals have an IGF1 concentration that is near or below the lower limit of normal for young healthy individuals. The observed decline in the GH/IGF1 axis appears to occur above the level of the pituitary because chronic treatment with GH-releasing hormone (GHRH), other GH secretagogues (GHS), or both mitigate much of the decline. The cause of the fall-off in GH/IGF1 axis activity is not clear but could be explained by age–related decreases in GHRH or ghrelin secretion, increased inhibition by somatostatin, increased sensitivity of somatotrophs to negative feedback inhibition by IGF1, a decline in pituitary responsiveness to GHRH or ghrelin, or a combination of any of these changes. Ghrelin appears to be the natural ligand for the GHS receptor. Although there is a close physiological relationship between GH secretion and slow-wave sleep, it is unclear if the altered GH/IGF1 axis is the consequence or cause of profound age–related changes in sleep architecture.

27. Is the decline in the GH/IGF1 axis related to age-related changes in body composition and function?

Many of the body composition changes and differences in physical and psychological function that occur with aging seem consistent with a GH/IGF1-deficient state. Indeed, the decrease in GH associated with aging is associated with many of the same physiological abnormalities seen in younger adults with GH deficiency, including:

- Reduced lean body mass and muscle mass
- Reduced strength and aerobic capacity
- Increased total, central, and intraabdominal (visceral) fat
- High incidence of metabolic syndrome
- Reduced bone mass and density
- Reduced or absent slow-wave (deep) sleep
- High incidence of mood disturbance (depression)
- Deterioration of memory and cognitive function

It remains unclear whether age–related GH/IGF1 changes cause these effects.

28. Is GH replacement recommended for healthy older adults?

There are no approved therapies for the age-related decline in GH. Although GH therapy in younger GH-deficient adults improves body composition, BMD, exercise capacity, cardiac function, cholesterol levels, and quality of life and may decrease mortality, the efficacy and safety of therapy for the otherwise "healthy" older adults are controversial. A 2007 systematic review of clinical trials of GH in healthy older adults concluded that therapy does increase IGF1 concentrations, although women may require higher doses of GH for longer periods than men to achieve physiologic replacement levels. Despite higher doses per kg body weight, women do not consistently demonstrate the increase in lean body mass or decrease in fat mass that occurs in men. Further, translation into clinically significant changes in strength, function, BMD, and improved metabolic parameters has been difficult to demonstrate in either sex. GH treatment is associated with several important adverse events compared to placebo, such as a significantly increased incidence of soft tissue edema (42%), carpal tunnel syndrome (18%), arthralgias (16%), gynecomastia (6%), impaired glucose tolerance (13%), and new onset of diabetes (4%).

29. What happens to the hypothalamic-pituitary-adrenal (HPA) axis with aging?

HPA axis activity changes with aging and is different between the sexes. The cortisol response to pharmacological stimuli and psychological stressors is augmented with aging in both men and women, but women have a more exaggerated response compared to men, suggesting that the loss of female sex hormones may contribute to alterations in HPA axis activity. However, distinguishing between the independent effects of age, declines in sex hormones, and body composition–related changes in the HPA axis is challenging. For example, morning cortisol levels tend to be lower, and stress-induced HPA axis responsiveness tends to be greater in older as compared with younger adults, but such findings are also associated with central obesity (commonly found with aging; see above). Additionally, dynamic HPA axis responses to various stressors have been reported to be exaggerated in postmenopausal compared to premenopausal women, with estradiol treatment attenuating the responses in postmenopausal women. However, several characteristics appear to be unique to aging. First, there is evidence for a phase advance characterized by an earlier morning cortisol peak. Second, the evening cortisol nadir appears to be higher in older persons, resulting in a compression of the diurnal amplitude. Third, glucocorticoid-mediated negative feedback is decreased. In total, mean 24-hour serum cortisol concentrations are 20–50% higher in both older women and men (see Table 63.2), likely reflecting alterations in glucocorticoid clearance, HPA axis responsiveness to stress, and central glucocorticoid-mediated negative feedback. Finally, suppression of ovarian hormones for 20 weeks with leuprolide did not alter basal or dynamic HPA axis activity in premenopausal women, but estrogen add-back treatment reduced dynamic HPA axis activity compared to preintervention levels, suggesting that aging, as opposed to the decline in ovarian hormones, is the predominant contributing factor to increased HPA axis activity in older women. However, further research is needed to tease out the complex interaction between sex hormone changes and aging effects on the HPA axis in both women and men.

Notably, glucocorticoid regulation may also occur at a local tissue level outside the influence of the HPA axis. The enzyme 11-beta hydroxysteroid dehydrogenase type 1 (11βHSD1) regenerates cortisol from inactive cortisone, and this enzyme has different expression in different tissues and with aging. The skin of aged individuals has shown higher 11βHSD1 activity, which could enhance cortisol-induced catabolism on skin tissue without affecting adrenal cortisol production. Aging may also affect the expression of the enzyme 11-beta hydroxysteroid dehydrogenase type 2 (11βHSD2), which is responsible for converting cortisol to inactive cortisone. How aging affects local glucocorticoid regulation by changing 11βHSD1 and 11βHSD2 expression in tissue is an area of investigation.

The clinical impact of cortisol on older adults remains unclear. A recent meta-analysis of four large UK-based cohort studies of older adults followed for 8 years showed no association of either morning cortisol levels or diurnal cortisol slope with mental well-being. Areas of ongoing research include the effect of the increase in the exposure to systemic or tissue-specific glucocorticoids in older adults on such age–related changes as central obesity, insulin resistance, decreased lean body mass, increased risk for fractures, decreased sleep quality, and poor memory.

30. What do thyroid function profiles look like in older adults?

Interpreting data from studies done in older adults regarding thyroid function is difficult because evaluation is often complicated by the increased prevalence of chronic disease and medication use. Nevertheless, serum thyroid-stimulating hormone (TSH) concentrations and distributions appear to increase with age (see Table 63.2) without any changes in free thyroxine (fT4) concentrations and independent of the presence of antithyroid antibodies. These findings suggest a natural shift to higher TSH levels with aging rather than an increased incidence of hypothyroidism. Hypotheses for these results include a decline in thyroid function or a recalibration of baseline TSH.

Studies have demonstrated reduced clearance of T4 and triiodothyronine (T3) in aging, and a resultant decrease in T4 and T3 production. Serum reverse T3 (rT3) concentrations appear to increase with age and the presence of disease. Higher levels of rT3 were associated with a lower physical function status. Although serum fT4 levels tend to remain stable, older individuals with higher fT4 levels were observed to have a lower physical function status and an increase in overall 4-year mortality. Total T3 levels were inversely related to physical performance and lean body mass. These trends in thyroid hormone levels may indicate that it is beneficial to have lower activity of the thyroid hormone axis in old age. Finally, in euthyroid individuals with TSH and fT4 concentrations within the reference range, T3 concentrations are lower in older individuals without acute illness than in younger individuals, possibly due to a decrease in 5'-deiodinase activity in aging.

Recognition of age-specific reference ranges would have important implications for defining subclinical hypothyroidism in older adults and treatment targets for thyroid hormone replacement.

31. What thyroid conditions are more prevalent with aging?

Thyroid nodules increase with age, with an estimated prevalence of 37–57%. The risk of malignancy in a nodule also increases with age; however, the prevalence of cancer may or may not be higher in adults aged >60 years depending on the population studied.

The most frequent cause of hyperthyroidism in older adults is toxic multinodular goiter rather than Graves' disease. Presenting symptoms of hyperthyroidism may be more atypical: apathy, anorexia, and atrial fibrillation are more common compared to younger adults while hyperadrenergic symptoms are less common. Overt hyperthyroidism due to comorbid conditions or medications is also more common in older adults.

Hypothyroidism increases significantly with age due to multiple conditions, including autoimmune thyroid dysfunction, use of medications, and nonthyroidal illness. The incidence of myxedema coma is also higher in older adults.

Subclinical hypothyroidism increases with age, but the actual incidence depends on the definition of upper limits of normal for TSH. For example, 15% of disease-free US adults over age 80 have TSH levels >4.5 mIU/L, but if the threshold were to change to TSH >2.5 mIU/L, the incidence would be as high as 40%.

32. Should subclinical hypothyroidism or subclinical hyperthyroidism be treated in older adults?

Subclinical hypothyroidism (TSH mildly elevated, T4 within the reference range) in individuals <65 years of age is associated with increased ischemic heart disease and cardiovascular mortality; however, in several meta-analyses of studies in older adults, these risks were not found. Furthermore, a large proportion of older adults (over 40%) may revert to euthyroidism after 4 years of follow-up without treatment. Some data suggest that levothyroxine treatment can be considered in older adults with either TSH >10 mIU/L and positive antithyroid antibodies or symptoms consistent with hypothyroidism, to reduce the risk of progression to overt hypothyroidism, decrease the risk of cardiovascular events, and improve quality of life. This leaves the question of what TSH level should be targeted in adults treated for overt hypothyroidism. The goal should be to avoid subclinical and overt hyperthyroidism; based on epidemiologic studies, a serum TSH level up to 10 mIU/L is a reasonable target in older adults.

A large proportion (approximately 40–50%) of older adults with subclinical hyperthyroidism (TSH low, T4, and T3 within the reference ranges) will also revert to euthyroidism with observation (within 2–7 years), while <10% will progress to overt hyperthyroidism. Some studies in high-risk older adults with persistent subclinical hyperthyroidism have showed increased risk for heart failure hospitalizations, nonfatal CVD, and dysrhythmias, whereas other studies have not shown an association with CVD mortality.

33. What factors should be considered when determining glycemic management of type 2 diabetes in older adults?

Over 25% of adults aged ≥65 years have diabetes and 50% of older adults have prediabetes. When managing diabetes in older adults, treatment decisions should be individualized and should consider age-related medical, psychological, functional, and social conditions for each person. Duration of diabetes, existent comorbidities such as heart disease or renal insufficiency, as well as polypharmacy and cost, are other important considerations. The 2024 American Diabetes Association's recommendations suggest that healthy older adults with diabetes who have few and stable comorbidities, intact cognitive function, and functional status should have lower glycemic goals (e.g., A1C <7.0–7.5%). On the other hand, they recommend that older adults with diabetes with significant cognitive and/or functional limitations, frailty, and severe comorbidities should have higher glycemic targets (e.g., A1C <8.0%). In older adults with very complex conditions or poor health, it is recommended to avoid reliance on A1C targets and focus on avoidance of hypoglycemia and symptomatic hyperglycemia. Older adults with diabetes have increased susceptibility to cognitive decline related to hypoglycemia and are at risk for overtreatment of diabetes. Individualized goals are essential. A glycemic target of <8.0% may be more prudent in managing diabetes in adults with long duration of diabetes, established cardiovascular disease, limited life expectancy, and particular susceptibility to severe hypoglycemia. Large multicentered studies that aimed for intense glycemic control of A1C <6.0–6.5% in older individuals showed no significant reduction in their primary combined cardiovascular endpoints but reported significantly more episodes of hypoglycemia in those individuals with intensive blood glucose management. Thus, the risks of intensive control likely outweigh the benefits in older adults. Given the increasing complexity of glucose management in type 2 diabetes as new medications and drug classes are developed, a patient-centered treatment plan is necessary for reconciling glycemic management and optimal patient outcomes.

34. What medications should be considered for the treatment of type 2 diabetes in older adults?

Special considerations are required in prescribing and monitoring diabetes medications in older adults. Metformin has traditionally been considered contraindicated when the estimated glomerular filtration rate (eGFR) is <60 mL/min; however, recent studies show that metformin can be used safely in adults with eGFR >30 mL/min (with suggested dose reduction by half with eGFR 30–45 mL/min). Because serum creatinine alone is often not an adequate reflection of GFR in older adults, it is important to assess the eGFR that also accounts for age and body weight. Metformin is still absolutely or relatively contraindicated for those with acute illness, hospitalization, severe renal impairment, congestive heart failure (CHF), and impaired hepatic function because of the potential risk of lactic acidosis.

Use of thiazolidinediones in older adults is generally not recommended for those at increased risk for CHF or peripheral fractures (older postmenopausal women). Furthermore, there is a modest cumulative dose-related increased risk of bladder cancer in people taking pioglitazone. Long-acting insulin secretagogues (glyburide) can cause hypoglycemia in older adults and are contraindicated. Shorter-acting insulin secretagogues (glipizide, glimepiride) should be used with caution, as older adults are particularly predisposed to hypoglycemia, especially those who skip meals.

GLP1-based therapies act in a glucose-dependent manner and are associated with less hypoglycemia. Dipeptidyl peptidase 4 (DPP4) inhibitors have the advantage of being orally dosed once daily, being weight neutral, and being safe for use (with dose adjustment) in those with renal impairment. There is concern for increased risk of CHF hospitalizations for adults using DPP4 inhibitors. GLP1 receptor agonist (GLP1 RA) therapy tends to cause gastrointestinal discomfort and leads to weight loss; therefore, balancing the potential risks and benefits in older adults is warranted, especially in individuals with low body weight. Though dosed once daily to once weekly, GLP1 RA injections require good visual and motor skills.

Insulin injections may also be problematic for the visually impaired person and require adequate cognitive ability of the patient or a caregiver. Overtreatment with or a mistimed dose of insulin can easily cause hypoglycemia. In older adults, hypoglycemia may be particularly hard to identify and may be incorrectly diagnosed as irreversible cognitive impairment. Management of diabetes medications can be improved in older adults with visual impairments through the use of devices such as glucometers with large easier-to-read screens, audio glucometers, magnifying glasses to help see syringes, or preloaded insulin pens.

The newer antidiabetes agents are the sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors). A meta-analysis of studies showed canagliflozin can be used safely in older adults with beneficial effects of lowering CVD risk, A1C, systolic blood pressure, and body weight. However, SGLT2 inhibitors are also associated with increased frequency of genital and urinary tract infections, and longer-term safety data are needed.

KEY POINTS

Hormones and Aging

- Most hormonal axes are associated with a gradual decline over time, beginning at about age 30 years, with the exception of the relatively rapid decline in estradiol two years prior to the final menstrual period in women.
- Serum total testosterone decreases gradually with age in men, but there are numerous other factors that can contribute to the decline, including health and lifestyle.
- By age 70 years, DHEA, a precursor for androgens and estrogens, is approximately 20% of peak levels observed in the third decade of life.
- The decline in GH with aging is accompanied by changes in body composition; however, whether GH deficiency contributes to the body composition changes or vice versa is unknown.
- Age-specific reference ranges for TSH may be appropriate and have important implications in defining subclinical hypothyroidism in older adults.

Take Home Messages: No Magic Hormonal Fountain of Youth

- Estrogen-based hormone therapy is controversial but is indicated as first-line therapy for relief of vasomotor and genitourinary symptoms, used in women with elevated risk for bone loss and fractures, as well as for those with hypoestrogenism caused by hypogonadism, surgical menopause, or premature ovarian insufficiency (POI). There may be cardiovascular benefits if therapy is initiated early (near menopause).
- Testosterone therapy for older hypogonadal men is associated with consistent improvements in body composition (decreased fat and increased fat-free mass), but instituting therapy requires close monitoring, especially in regard to cardiovascular status. Consistent evidence for improvement in strength or function is not available. Testosterone therapy is only indicated for men with signs and symptoms of androgen deficiency and unequivocally and consistently low morning serum testosterone levels.
- DHEA replacement therapy increases levels of estradiol, testosterone (women only), IGF1, and bone mineral density but does not appear to be associated with clear improvements in metabolism or body composition in older humans.
- There are no FDA-approved medications for GH supplementation in adults with age–related declines in GH production. GH supplementation appears to increase lean body mass more in older men than in women. These changes have not translated into functional improvements, and treatment is associated with high rates of adverse events.
- Physical activity and long-term caloric restriction have the best evidence for ameliorating age-related increases in adiposity, reductions in lean body mass, and CVD risk factors.
- Weight loss in older adults with obesity is associated with improvements in CVD risk factors, but exercise may be needed to attenuate loss of muscle and bone mass during weight loss and mitigate against frailty.
- Adequate calcium and vitamin D are essential for fall and fracture prevention and maintenance of bone mineral density.
- Clinicians caring for older adults with type 2 diabetes must take into consideration the clinical and functional heterogeneity of their patients when setting and prioritizing an individual's treatment goals and drug regimen. Occult hypoglycemia may be much more common in older adults, especially those treated with insulin and sulfonylureas, and the consequences of this on the central nervous system and cardiovascular function must be carefully considered.

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CHAPTER 64

Endocrinopathies Due to Immune Checkpoint Inhibitors

Chermaine Hung, David R. Saxon, and Thomas J. Jensen

1. How are immune checkpoint inhibitors (ICPis) classified? Explain their mechanisms of action.

ICPis have been developed against cytotoxic T-lymphocyte associated protein 4 (CTLA4), programmed cell death protein 1 (PD1), programmed death ligand 1 (PDL1), and lymphocyte-activation gene 3 (LAG-3). These proteins play an important role in the development of peripheral tolerance and prevention of autoimmunity. Antigen presenting cells (APC) activate T cells through the binding of antigens (either foreign from infections, or mutated self from cancer cells) on major histocompatibility complexes with the T-cell receptor but require additional stimulation. CTLA4 and PDL1 receptors on the T cell are part of a complex system of checkpoints that promote peripheral tolerance. CTLA4 is the primary receptor that prevents activation of naïve T cells in lymph nodes and competes with its homolog receptor on the T cell, CD28, for binding of CD80/CD86 on the APC. Binding of CD28 promotes activation and proliferation while binding of CTLA4 leads to anergy and reduced survival. PD1 regulates previously activated T cells in the periphery and interacts with receptor PDL1 or programmed death-ligand 2 (PDL2) on peripheral cells to further promote self-tolerance through reduced T-cell activation and survival known as T-cell exhaustion. LAG-3 is a newer immunotherapy target that inhibits T-cell activation and function by interacting with major histocompatibility complex class II. It may interact with T-cell antigen receptor-CD3 complex and other ligands such as fibrinogen-like protein 1 to suppress autoimmunity. T cells that express LAG3 therefore have been activated at one point but now show exhaustion. LAG3 has become an attractive target because of the hope to reactivate T cells that already were targeting cancer cells but have gone through exhaustion while not activating naïve T cells like CTLA4, which may increase the risk of targeting off target tissues leading to side effects.[1] Cancer cells have found ways to take advantage of this peripheral tolerance system to evade the immune system. ICPis block these normal protein interactions, thereby removing the “brakes” on the immune system and resulting in enhanced T-cell-mediated death of cancer cells (Fig. 64.1), as well as the adverse endocrinopathies addressed below.

2. What ICPis are available in the United States? What are the indications for the use for these various medications?

Several ICPis are currently approved by the US Food and Drug Administration.[2] The first agent approved for use in patients with advanced melanoma was ipilimumab, a CTLA4 inhibitor. Available PD1 inhibitors are nivolumab, pembrolizumab, dostarlimab, cemiplimab, and toripalimab. Nivolumab is approved for patients with metastatic melanoma, previously treated metastatic non–small cell lung cancer (NSCLC), small-cell lung cancer (if progressed on platinum-based and another therapy), recurrent or metastatic squamous cell carcinoma of the head and neck, advanced renal cell carcinoma (often in combination with ipilimumab), hepatocellular carcinoma (previously treated with sorafenib), relapsed or progressive classical Hodgkin lymphoma (after auto-HSCT), unresectable or metastatic urothelial cancer, and certain cases of metastatic colon carcinoma. Pembrolizumab is approved for advanced melanoma, advanced NSCLC, head and neck squamous cell cancer, classical Hodgkin lymphoma, relapsed or refractory primary mediastinal large B-cell lymphoma, advanced urothelial cancer, tumors that have microsatellite instability-high (MSI-H) or are mismatch repair deficient (dMMR), advanced cervical cancers, hepatocellular carcinoma (previously treated with sorafenib), Merkell cell carcinoma, and advanced gastric adenocarcinoma. Dostarlimab is approved for use in mismatch-repair advanced endometrial cancer, as well as certain dMMR solid tumors. Cemiplimab is approved for metastatic or advanced cutaneous squamous cell carcinoma and basal cell carcinoma and certain types of NSCLC. Toripalimab was approved for advanced nasopharyngeal carcinoma. Available PDL1 inhibitors are atezolizumab (approved for urothelial cancers and NSCLC), durvalumab (approved for urothelial cancers and

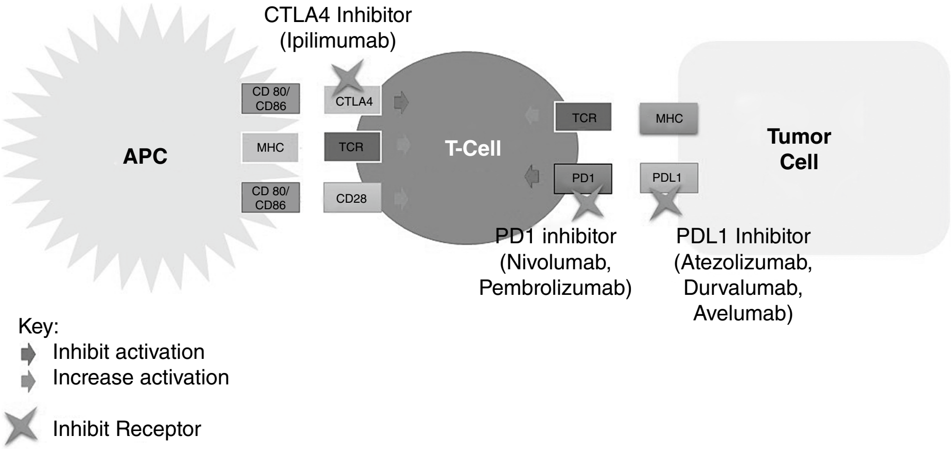

Fig. 64.1 Mechanism of immune checkpoint therapy in cancer treatment.

stage III NSCLC), and avelumab (approved for Merkel cell carcinoma and urothelial carcinoma). The first FDA-approved LAG3 inhibitor is relatlimab, which is currently used in conjunction with nivolumab for advanced melanoma. Nivolumab is approved in combination with ipilimumab in certain situations for the treatment of metastatic colorectal cancer, renal cell carcinoma, NSCLC, malignant pleural mesothelioma, and hepatocellular carcinoma. Pembrolizumab or avelumab can be used in combination with axitinib for metastatic renal cell cancer. Atezolizumab is approved for use with paclitaxel for certain triple-negative breast cancers; also with carboplatin and etoposide for small-cell lung cancers. Indications for the use of these therapies are rapidly changing, and multiple drug combinations are being tested in a variety of cancers.

3. What is the spectrum of immune–related adverse events seen with ICPis?

Immune–related adverse events (irAEs) affect multiple organs and systems including the skin, GI tract, lungs, kidneys, heart, eyes, endocrine system, musculoskeletal system, nervous system, and hematology system.

4. What specific endocrine disorders are seen with ICPis?

The most common endocrinopathies associated with ICPis are acute hypophysitis (with accompanying central adrenal insufficiency, central hypothyroidism, and hypogonadotropic hypogonadism) and thyroid dysfunction. Additional endocrinopathies can include primary adrenal insufficiency, type 1 diabetes, autoimmune polyendocrine syndrome, and hypoparathyroidism, though these are rarer. Risk for development of these endocrinopathies is related to the type of ICPi, the dose, and whether combination ICPi therapy is used. Certain human leukocyte antigen (HLA) haplotypes have been associated with the development of ICPi–related endocrinopathies including type 1 diabetes, hypothyroidism, hypophysitis, and autoimmune polyglandular syndrome. HLA genotyping is being developed as a tool to predict the development of endocrine irAEs.[3] In addition, younger age (<65) compared to older age (≥75) also appears to be another risk for endocrine irAEs.[4] Sex differences have also been noted with men at higher risk for both hypophysitis[5] and primary adrenal insufficiency[6] whereas women are more likely to develop hypothyroidism.[7]

5. How are organ-specific toxicities due to immunotherapies graded?

The NCI Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology used for adverse event (AE) reporting. A grade refers to the severity of an AE and a general guideline is used to grade AEs on a scale of 1 through 5. Grade 1 AEs are defined as having mild or no symptoms and can be clinically monitored without intervention. Grade 2 AEs are moderate and limit age-appropriate activities of daily living (ADL); minimal, local, or noninvasive intervention is indicated. Grade 3 AEs are severe but not immediately life-threatening; they limit self-care

ADL, and hospitalization is generally needed. Grade 4 AEs have life-threatening consequences and urgent intervention is needed. A grade 5 AE is one that leads to a patient's death.

6. What is the overall incidence of clinically significant endocrinopathies in patients treated with ICPis?

According to a systematic review and metaanalysis that included 7551 patients in 38 randomized trials, the incidence of endocrinopathies with ICPis was approximately 10% overall.[8]

7. What are the rates of various endocrine irAEs?

Table 64.1 highlights the overall incidence of various endocrinopathies due to ICPis. Differences in adverse event rates are based on whether a CTLA4 or PD1 inhibitor or combination therapy is used.

8. How does management of grade 4 endocrine toxicities differ from grade 4 nonendocrine toxicities?

Whereas with nonendocrine toxicities the offending agent should be permanently discontinued, grade 4 endocrine toxicities should be managed with hormone replacement and in many cases, the medication can be continued.

9. What previously rare pituitary problem is seen with ICPis? Which medication is it most commonly seen with? How does it present clinically?

Hypophysitis or inflammation of the pituitary gland leading to pituitary dysfunction is seen rather frequently with certain ICPis. Imaging often shows pituitary enlargement, which may be subtle and only evident if pretreatment imaging is available as a comparison. Common symptoms of hypophysitis include headache, weakness, and fatigue. Vision changes are less common.[9] The most commonly seen hormonal problem is central hypothyroidism followed by central adrenal insufficiency and hypogonadotropic hypogonadism. Prolactin levels are often low and growth hormone is relatively spared. Imaging may demonstrate initial changes such as pituitary gland or stalk enlargement, but findings can be subtle or transient. Later changes include a decrease in

TABLE 64.1 Incidence of Any Grade Endocrinopathy Due to ICI When Used Alone or in Combination

ICI TYPE	HYPOPHYSITIS	HYPOTHYROIDISM	HYPERTHYROIDISM	ADRENAL INSUFFICIENCY	INSULIN-DEPENDENT DIABETES
PD1	0.21% (0.08 – 0.39), p < 0.0001	7.99% (6.33 – 9.92), p < 0.0001	2.65% (1.64 – 3.87), p < 0.0001	0.252% (0.123 – 0.422), p < 0.0001	0.13% (0.032 –0.272), p = 0.0004
PDL1	0.0008%, (<0.0001 – 0.06), p = 0.95	8.88% (6.78 – 11.21), p < 0.0001	2.04% (0.93 – 3.53), p < 0.0001	0.101% (0.0002 – 0.316), p < 0.0001	0.07% (<0.0001 –0.408), p = 0.268
CTLA4	2.77% (0.0016 – 9.05), p = 0.0489	1.82% (0.25–4.44), p = 0.0049	<0.0001% (< 0.0001 – 0.046), p < 0.0001	0.289% (<0.0001 – 1.071), p = 0.102	<0.0001% (<0.0001–0.027), p < 0.0001
PD1 + CTLA4	1.17% (<0.0001 = 3.84), p = 0.056	10.28% (2.64 – 21.86), p = 0.0033	4.51% (0.18 – 13.18), p = 0.022	0.551% (<0.0001 – 1.840), p = 0.069	0.078% (<0.0001 – 0.656), p = 0.436
PDL1 + CTLA4	0.52% (0.03 – 1.40), p = 0.0145	7.64% (6.23 – 9.17), p < 0.0001	2.93% (1.63 – 4.56), p < 0.0001	1.867% (0.844 – 4.232), p < 0.0001	0.27% (<0.0001 – 1.001), p = 0.0999

ICI, Immune Checkpoint Inhibitors; *PD1,* programmed cell death protein 1; *PDL1,* programmed death ligand 1; *CTLA4,* cytotoxic T-lymphocyte associated protein 4.
Adapted from Vardarli et al.[28]

pituitary volume or empty sella.[9] Posterior pituitary involvement is rare, with ICPi–related arginine vasopressin deficiency occurring in 0.7–1.4% of patients. It can occur alone or in the context of hypophysitis, and has been related to use of PD1, PDL1, or CTLA4 inhibitors.[10] Ipilimumab by itself or in combination with nivolumab has the highest incidence of hypophysitis occurring on average in 3.2% and 6.4% of patients, respectively, usually happening 8–12 weeks after initiation of medication. This is thought to be due in part to the pituitary gland cells having a higher level of CTLA4, which leads to complement activation. The incidence appears less with PD1 and PDL1 inhibitors as noted below in Table 64.1.

10. What is the management for ICPi–related hypophysitis?

Patients with central adrenal insufficiency should be treated with corticosteroids promptly and prior to other replacement hormones, especially thyroid hormone, as treatment first with thyroid hormone may precipitate adrenal crisis.[11] There has been a question whether to treat with high-dose corticosteroids (prednisone 1 mg/kg) compared to physiological dosing. Recent studies have shown that high-dose steroids fail to improve resolution of pituitary enlargement and pituitary insufficiency and may promote central adrenal insufficiency (if not present prior).[12] High-dose steroids could be considered for patients with severe pituitary swelling, especially if there was risk for optic nerve compression and should be given initially if a patient presents in adrenal crisis. Patients with central hypothyroidism (determined by a low free T4 with or without a low T3) may be placed on thyroid replacement medication once adrenal status has been determined to be normal or after replacement has begun. Treatment goals for central hypothyroidism are based on free T4 levels being in the midrange of the particular lab assay. Appropriate sex hormone replacement in hypogonadotropic hypogonadism patients (males with testosterone and premenopausal females with estrogen and progesterone as needed) can be considered as well. It should be noted that in one long-term follow up study (median 33 months), 85% of patients with central hypothyroidism and 84% of patients with hypogonadism had recovered function while corticotroph deficiency rarely recovers. Therefore, patients with thyroid or gonadal dysfunction can be monitored for recovery if asymptomatic, or if started on medication, should be tapered off to see if the respective axis has recovered. Patients with central adrenal insufficiency on physiologic replacement could be rechecked by holding their steroid for a day or two with evaluation of baseline adrenal labs as well as performing a cosyntropin stimulation test; however, in most case lifelong replacement therapy will be necessary.

11. What thyroid disorders are associated with ICPis use? How are they differentiated and how are they managed?

A recent study showed that approximately 30% of patients on ICPis had new-onset abnormal thyroid function tests and an additional 70% with thyroid test abnormalities at baseline had exacerbation on lab testing at a median time point of 33–46 days after starting treatment. Due to variation in definitions of hypothyroidism, hyperthyroidism, and thyrotoxicosis, it can be hard to delineate the true incidence of these conditions in clinical trials and practice. A recent review found the incidence of ipilimumab–related hypothyroidism to be roughly 5.6% and thyroiditis to be 3.2%; with PD1 inhibitors, the rates of hypothyroidism were 5.9% and of hyperthyroidism were 3.3%; and with PDL1 inhibitors, the hypothyroidism incidence was 4.3%. Overall PDL1 inhibitors tend to have lower rates of thyroid disease, particularly hypothyroidism.[13] The incidence of hypothyroidism was <5% in patients on LAG3 inhibitors.[14] The overall incidence of ICPi–related thyroid disease when receiving combination therapy (CTLA4 + PD1) jumps to 13.9% for hypothyroidism, 8% for hyperthyroidism, and 16.9% for other thyroid disorders including destructive thyroiditis.

12. What is the differential diagnosis for an elevated TSH and a normal or low free T4 in the setting of ICPi therapy?

Primary hypothyroidism should be suspected in the setting of an elevated serum TSH with a normal or low free T4 (fT4); however, this thyroid test pattern can also be seen in the hypothyroid phase of destructive thyroiditis. An enlarged thyroid and positive thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) suggest autoimmune hypothyroidism while normal gland size and negative antibodies would favor thyroiditis. When findings are equivocal, follow-up labs in 3–4 weeks may help determine if a recovering thyroiditis is present.

13. What thyroid disorders should be considered when TSH is suppressed and thyroid hormone levels are normal or elevated in the setting of ICPi therapy?

Suppressed TSH with normal or elevated thyroid hormones would suggest autoimmune hyperthyroidism (Graves' disease) or the hyperthyroid phase of destructive thyroiditis. Patients with autoimmune hyperthyroidism tend to have an enlarged thyroid, elevated thyroid stimulating immunoglobulins (TSI) or positive thyrotropin receptor antibodies (TRAB), and increased homogenous uptake on I-123 (RAI) scan while patients with destructive thyroiditis tend to have normal size gland, normal TSI or TRAB levels, and decreased uptake on I-123 scan. The clinician should also be aware of other underlying causes of thyroid dysfunction either from medications like amiodarone or lithium, or iodinated contrast that may exacerbate underlying thyroid disease as well as limit the utility of I-123 scans if used recently. In addition, central hypothyroidism can occur especially in the setting of CTLA4 inhibitor use.

14. How should hypothyroidism be monitored and managed in the setting of ICPi therapy?

Monitoring and treatment of these toxicities are essential. The American Society of Clinical Oncology recommends testing TSH and fT4 every 4–6 weeks as part of routine clinical monitoring or for case detection in symptomatic patients on therapy.[15] For primary hypothyroidism, a grade 1 toxicity is a TSH <10 mIU/L in an asymptomatic patient; it is recommended that ICPi therapy is continued with close monitoring of both TSH and free T4. Grade 2 toxicity is when the TSH is persistently >10 mIU/L and moderate symptoms are present but the patient can still perform ADLs. In this scenario ICPi therapy may need to be held temporarily until symptoms improve, thyroid hormone replacement should be prescribed, and TSH should be monitored every 6–8 weeks while titrating hormone replacement (or alternatively fT4 can be used up to every 2 weeks to titrate hormone replacement if the fT4 was initially low). Grade 3 or 4 toxicity is defined as severe hypothyroid symptoms with medically significant or life-threatening consequences that prevent a patient from performing ADLs. ICPi therapy should be held in such cases until symptoms resolve with treatment and the patient should be admitted and given IV thyroid hormone replacement if signs of myxedema are present (i.e., hypothermia, bradycardia). Prior to initiation of thyroid medication, all patients should have their adrenal axis assessed to rule out the presence of adrenal insufficiency that may be exacerbated if untreated prior to initiation of thyroid hormone.[12]

15. How should hyperthyroidism be managed in the setting of ICPi therapy?

Patients with destructive thyroiditis who are asymptomatic can be monitored while those with significant symptoms (palpitations, tremors) can be treated with beta-blockers and, if necessary, steroids. If and when patients convert to a hypothyroid phase, monitoring can be done with serial thyroid labs every 4–6 weeks if asymptomatic or patients can be placed on thyroid hormone replacement to titrate to goal TSH. After several months (4–8 months), a trial without medication can be done to determine if the patient still requires treatment. Patients with clinical autoimmune hyperthyroidism (suppressed TSH and elevated thyroid hormones) can be treated with antithyroid medications (methimazole or propylthiouracil) and beta blockers as necessary. If grade 3 or 4 toxicity occurs, ICPis should be held and the patient hospitalized as necessary until stabilized. In addition, avoidance of things that may exacerbate thyroid disease, such as iodinated contrast, is recommended until the patient is placed on medications that will control thyroid disease. Treatment with I-131 RAI or thyroidectomy can also be considered.

16. What other thyroid abnormalities can be seen in patients on ICPis?

Finally, a normal or mildly low TSH along with normal or low fT4 and frankly low T3 suggests nonthyroidal illness (euthyroid sick syndrome). Patients should not be given thyroid supplementation, but rather have their thyroid labs monitored.

17. What other endocrinopathies have been seen with ICPis?

Primary adrenal insufficiency, type 1 diabetes, and hypoparathyroidism have been rarely seen with the use of ICPis. Primary adrenal insufficiency should be suspected in the setting of typical symptoms of adrenal insufficiency (fatigue, light headedness, weight loss, abdominal pain, nausea, vomiting), with an elevated adrenocorticotropic hormone (ACTH), and low cortisol, especially

<3 ug/dL, or a failure to stimulate cortisol to 14–15 ug/dL or greater during a cosyntropin stimulation test (depending on assay).[16] Patients with primary adrenal insufficiency need both glucocorticoid and mineralocorticoid supplementation, whereas those with central adrenal insufficiency only require glucocorticoid replacement.

New type 1 diabetes should be considered in patients with sudden onset of diabetes, especially if they present with diabetic ketoacidosis (DKA). Antibodies for type 1 diabetes along with C-peptide and insulin levels can help differentiate type 1 from type 2 diabetes, although in ICPi–related diabetes not all patients test positive for antibodies (e.g., antiglutamic acid decarboxylase). The incidence of ICPi–related type 1 diabetes is <1%, with a variable onset after treatment initiation, and a median time to diagnosis of 7–25 weeks.[17] About 30% of patients may present in DKA or with pancreatitis,[18] and the majority of patients require lifelong treatment with insulin.

Hypoparathyroidism presents with symptoms of hypocalcemia (numbness, tingling, tetany) and can be treated with a combination of calcium, vitamin D analogs (calcitriol), and parathyroid hormone, if necessary. Primary orchitis has been described in case reports. The natural history of these disorders is limited due to rare occurrences at this time. Autoimmune polyglandular syndrome (APGS) is a rare phenomenon, and thus it is difficult to determine the incidence; but in a review article of 23 patients presenting with APGS 2, the median time to onset was 8.5 weeks with thyroid disease (18/23, 78.3%), type 1 diabetes (17/23, 73.9%), hypophysitis (11/23, 47.8%), and adrenal insufficiency (2/23, 8.7%).[19]

18. What is the most frequently reported adverse event with PD1 and PDL1 inhibitors?

Fatigue is the most commonly reported adverse event with these agents and the pathogenesis is poorly understood. Individual drug studies report fatigue in 16–37% of patients on PD1 inhibitors and 12–24% of patients on PDL1 inhibitors. Therefore, of the patients who report fatigue with these agents, only a minority of them will have hypothyroidism or adrenal insufficiency as the cause. Regardless, patients with even subtle changes in energy level should have adrenal and thyroid labs analyzed to look for potential endocrinopathies.

19. How much more likely are patients to develop thyroid dysfunction when taking a combination of ipilimumab (CTLA4 inhibitor) plus a PD1 inhibitor than when taking ipilimumab alone?

Patients taking combination therapy are approximately 3.8 times more likely to develop hypothyroidism and 4.2 times more likely to develop hyperthyroidism than when given ipilimumab alone.

20. How relatively likely are other endocrinopathies when comparing different classes of ICPis?

Patients on PD1 inhibitors are about twice as likely to develop hypothyroidism compared to patients on ipilimumab. PD1 inhibitor therapy is about five times more likely to cause hyperthyroidism than PDL1 inhibitor therapy, but hypothyroidism rates are similar. Patients on ipilimumab are about five times more likely to develop hypophysitis compared to PD1 inhibitor therapy alone, but those who are on a combination of these drugs are more than twice as likely to develop hypophysitis compared to ipilimumab alone. Actual rates of endocrinopathies when combining PD1 inhibitors with LAG3 inhibitors is limited due to fewer studies (and hence comparing to other combinations), but in a study of melanoma patients, addition of the LAG3 inhibitor, relatlimab, increased rates of hypothyroidism/thyroiditis (18.0% versus 13.9%), adrenal insufficiency (4.2% versus 0.8%), and hypophysitis (2.5% versus 0.8%), while rates of hyperthyroidism were similar (6.2% versus 6.7%).[20]

21. Does the development of irAEs suggest improved cancer treatment outcomes compared to those who do not develop irAEs?

Current data suggest that the occurrence of an irAE predicts a better cancer response to treatment. The hypothesis is that the occurrence of an irAE indicates better activation of the immune system. A meta-analysis with nivolumab in the treatment of melanoma showed a slightly better objective response rate (ORR) (44%) for those receiving immune modulating (IM) agents to treat irAEs compared to those who did not receive IM (36%). Another study with ipilimumab in melanoma showed that early irAEs predicted a better probability of ORR, with all patients who achieved complete response having more severe irAEs. In patients treated with pembrolizumab for melanoma, the development of vitiligo was also a predictor of ORR. Patients who developed early irAEs while being treated for NSCLC with nivolumab showed a better objective response (37% versus 17%) and longer progression free survival (PFS) (6.4 months versus 1.5 months). A metaanalysis including studies on PD1, PDL1, and CTLA4 reported that the development of thyroid irAEs is associated with increased overall survival (OS) and PFS.[21] A retrospective study identified an increased rate of adequate cancer response in patients who developed an endocrine irAE compared to those who did not (45% versus 28.3%).[22] In addition, a metaanalysis based on tumor type reported a positive association between irAE occurrence and ORR, PFS, and OS regardless of the tumor type or ICPi used; grade 3 and 4 irAEs were associated with an improved ORR, but a worse OS.[23] Further studies to look at the exact nature and mechanism of this relationship are needed.

22. Are any ICPis being investigated for the treatment of thyroid cancer?

Small, ongoing clinical trials testing CTLA4, PD1, and PDL1 inhibitors are underway in combination with other treatment modalities in patients with anaplastic, poorly differentiated, and recurrent differentiated thyroid cancers. A recent case series evaluated pembrolizumab or nivolumab use in patients with metastatic anaplastic thyroid cancer, demonstrating a response to treatment in 16% and PFS of 1.9 months.[24] Combination therapy with ICPis for this population is being studied. In a case report, a patient with anaplastic thyroid cancer showing BRAF and programmed death-ligand 1 (PDL1) positivity had complete clinical and radiographic remission 20 months following treatment with vemurafenib and nivolumab.[25] There are also some ongoing investigations looking at ICPis use in medullary thyroid cancer.[26]

KEY POINTS

- The use of ICPis to treat advanced cancers is growing, and these agents have the potential to cause a variety of endocrinopathies. Available medications fall into three classes: cytotoxic T-lymphocyte–associated-protein 4 (CTLA4), programmed cell death protein 1 (PD1), and programmed death ligand 1 (PDL1) inhibitors.
- The most common endocrinopathies associated with ICPis are acute hypophysitis (with accompanying central adrenal insufficiency, central hypothyroidism, and hypogonadotropic hypogonadism) and thyroid dysfunction.
- The overall incidence of endocrinopathies with ICPis is approximately 10%.
- Hypophysitis, or inflammation of the pituitary gland and stalk leading to pituitary dysfunction, is a previously rare pituitary problem that is seen relatively frequently with ICPis (most commonly with ipilimumab). Single or multiple hormonal deficiencies can be seen with hypophysitis.
- Thyroid abnormalities that may be encountered when taking care of patients on ICPis include primary hypothyroidism, Graves' disease, thyroiditis, and euthyroid sick syndrome.

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CHAPTER 65

Thyroid and Parathyroid Surgery

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THYROID

1. Using the Bethesda System, list the possible results of fine-needle aspiration (FNA) of thyroid nodules and describe the appropriate surgical intervention.

The Bethesda System was updated in 2023. The most recent update simplified the terminology used to describe Bethesda III and Bethesda IV. The terms "follicular lesion of undetermined significance" and "suspicious for follicular neoplasm" to describe Bethesda III and IV, respectively, have been discontinued to avoid confusion.

- Nondiagnostic: Repeat FNA with ultrasound guidance. Thyroid lobectomy if still nondiagnostic.
- Benign: The risk of cancer is <5%. Clinical follow-up is appropriate.
- Atypia of Undetermined Significance (AUS): Risk of cancer 10–40%. Options include observation (if determined to be low-risk by ultrasound appearance and other clinical factors), and repeat FNA with or without molecular testing or surgery.
- Follicular Neoplasm: Risk of cancer 15–35%. Options include repeat FNA for molecular testing or surgery.
- Suspicious for malignancy: Risk of cancer 60–75%. Surgery for either thyroid lobectomy or thyroidectomy.
- Malignant: Risk of cancer >97%. Surgery for thyroid lobectomy or thyroidectomy is generally recommended; however, active surveillance can be considered in patients with very low-risk cancers (<1 cm, no evidence of invasion, metastasis, or aggressive features) or in patients with high-surgical risk or short expected remaining life spans due to comorbidities.

2. A patient underwent a thyroid lobectomy for a suspicious thyroid nodule, and the final pathology revealed carcinoma. How do you decide whether a completion thyroidectomy is necessary?

Patients undergoing lobectomy for an indeterminate/suspicious thyroid nodule should be counseled that a second surgery for completion of thyroidectomy may be necessary in some cases. In brief, a completion of thyroidectomy would be indicated if a thyroidectomy would have been recommended had the final diagnosis been available prior to the thyroid lobectomy. A lobectomy may be sufficient treatment for low-risk patients who meet the following criteria: unifocal tumor <4 cm without invasion and no regional or distant metastases. For high-risk and some intermediate-risk patients, completion of thyroidectomy is indicated to enable radioactive iodine therapy or to facilitate follow-up based on individual patient characteristics and preferences.

3. Why not just do an intraoperative frozen section on indeterminate thyroid nodules to help guide the extent of surgery?

Unfortunately, the accuracy of frozen section for most thyroid nodules is not much better than FNA and is therefore not routinely used. To distinguish a benign from malignant follicular thyroid lesion requires a detailed assessment for capsular and/or vascular invasion which cannot practically be accomplished intraoperatively. A frozen section can sometimes be useful for the definitive diagnosis of cancer in nodules that are in the suspicious category (Bethesda V).

4. What is the role of molecular testing of thyroid nodules?

Fifteen to thirty percent of thyroid nodules are cytologically indeterminate on FNA (Bethesda III and IV), and the majority (60–85%) of these nodules are benign. The goal of molecular diagnostic testing of thyroid nodules is to further stratify the risk of malignancy in those with indeterminate cytology to decrease the number of patients who undergo unnecessary surgery for benign disease. There are multiple commercially available tests that analyze for the genetic mutations/alterations and/or gene expression profiles known to occur in thyroid cancer. While not perfect, some of these tests are reported to have excellent negative predictive (95%) and reasonable positive predictive (50–70%) values. When appropriately utilized, these tests can safely and cost-effectively avoid unnecessary surgery in up to 20% of patients with indeterminate thyroid nodules.

5. What is the difference between total, near-total, and subtotal thyroidectomy?

A total thyroidectomy removes all grossly visible thyroid tissue. A near-total thyroidectomy removes all grossly visible thyroid tissue except for a small amount (<1 g) adjacent to where the recurrent laryngeal nerve enters the larynx. A total and near-total thyroidectomy have equivalent oncologic outcomes and are often considered synonymous. A subtotal thyroidectomy leaves more than 1 g of thyroid tissue and is not an appropriate cancer operation. It is used occasionally in patients with benign multinodular goiter or hyperthyroidism in an attempt to leave enough thyroid so that thyroid hormone replacement is not required. However, subtotal thyroidectomy for hyperthyroidism significantly increases the risk of recurrent hyperthyroidism (8%) compared to near-total/total thyroidectomy (0%) and is generally not recommended.

6. What is the appropriate extent of thyroidectomy for differentiated thyroid carcinoma?

For differentiated (papillary, follicular, and Oncocytic [formerly Hurthle] cell) cancers, the extent of surgery is determined by tumor size, presence of extrathyroidal extension, and regional or distant metastasis. For low-risk micro-carcinomas (<1 cm, no invasion or evidence of nodal/distant metastasis), active surveillance may be considered; otherwise, a thyroid lobectomy should be performed. Multiple studies have found that in properly selected low- to intermediate-risk patients, thyroid lobectomy and thyroidectomy have equivalent outcomes. Therefore, the initial surgical procedure for unifocal tumors 1–4 cm in size without extrathyroidal extension and without nodal/distant metastasis can be *either* thyroidectomy *or* thyroid lobectomy. Factors that might lead to thyroidectomy being chosen over lobectomy include older age (>55), significant contralateral nodules, history of radiation exposure, family history of thyroid cancer, or potential need for radioactive iodine. For high-risk tumors (>4 cm, gross invasion, clinically apparent nodal/distant metastases), a thyroidectomy is indicated.

7. What is the incidence of lymph node metastasis in differentiated thyroid cancer and when is a neck dissection indicated?

Differentiated thyroid cancer (predominantly papillary) involves cervical lymph nodes in 30–80% of cases. In the majority of cases, the metastatic nodes are not clinically evident; therefore, all patients should undergo preoperative full-neck ultrasound to assess for abnormal nodes. Unlike many other malignancies, the presence of *occult* lymph node metastases does not worsen the outcome for most patients with differentiated thyroid cancer, and routine prophylactic neck dissection does not clearly improve survival. Moreover, neck dissection may increase the risk of complications. For these reasons, prophylactic neck dissection for differentiated thyroid cancer is generally not recommended. The following are some general guidelines:

- All patients with clinically palpable, biopsy-proven nodes require a compartment (central and/or lateral) dissection at the same time as thyroidectomy.
- Any suspicious nodes on ultrasound should undergo FNA and, if positive, should be removed via formal neck dissection as above.
- Physical exam, ultrasound, and intraoperative assessment are insensitive in detecting nodal metastases in the central neck. It has been debated whether a *prophylactic* central neck dissection at the time of thyroidectomy is indicated for papillary carcinoma. The current American Thyroid Association (ATA) Guidelines state that prophylactic central neck dissection may be indicated in those with advanced tumors (>4 cm and/or grossly invasive) or if there are known lateral nodal or distant metastases. Thyroidectomy alone may be appropriate for noninvasive tumors <4 cm.

8. What is a central and modified radical neck dissection?

Central neck dissection removes all the perithyroidal and tracheoesophageal groove nodes (level VI) from the hyoid bone superiorly down to the sternal notch. Laterally, the dissection extends from the carotid-to-carotid artery. The lateral spread of disease usually involves the jugular lymph nodes (levels II–IV) and, less commonly, posterior (level V) nodes. A modified radical neck dissection, sometimes referred to as a functional dissection, removes all lymphatic tissue from levels II–IV (and sometimes level V) and spares the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve because sacrificing these structures (radical neck dissection) does not improve outcome.

9. Describe the appropriate surgical management for medullary thyroid carcinoma.

Medullary thyroid carcinoma accounts for less than 5% of thyroid cancers but occurs as part of an inherited syndrome in 20–25% of cases. Thus, all patients with medullary thyroid carcinoma should be considered for genetic testing. If the patient has MEN2 syndrome, then a prophylactic thyroidectomy is indicated, and the specific mutation in the *RET* gene can help determine at what age the surgery should occur. MEN2 patients should also be screened for pheochromocytoma and primary hyperparathyroidism so that these conditions can be surgically corrected prior to or concomitant with the thyroidectomy, respectively. Because medullary thyroid cancer is not sensitive to radioiodine or thyroid-stimulating hormone (TSH) suppression, a total thyroidectomy is indicated. Due to the high incidence of regional lymph node involvement, a central neck dissection is performed at the time of thyroidectomy. Some surgeons also advocate routine prophylactic ipsilateral or bilateral modified radical neck dissection at the initial surgery; however, despite this aggressive approach, a biochemical cure (normalization of calcitonin) is uncommon in patients with positive nodes. In the latest ATA guidelines, the task force did not achieve consensus. Some recommend that lateral neck dissection should only be performed *selectively* based on clinically or ultrasonographically abnormal nodes. Others consider basal serum calcitonin levels, recommending the addition of prophylactic ipsilateral central and lateral neck dissection for levels >20 pg/mL and bilateral lateral dissection for levels >200 pg/mL.

10. Discuss the role of surgery in anaplastic carcinoma of the thyroid.

Anaplastic carcinoma of the thyroid accounts for less than 1% of thyroid cancers but is one of the most aggressive solid tumors known and is rarely curable. Median survival is about 6 months. At the time of diagnosis, 50% of patients harbor distant metastases and 95% have local invasion, precluding a curative resection. Thus, surgery is usually restricted to a diagnostic or palliative role. An incisional biopsy of the thyroid is sometimes necessary to differentiate anaplastic cancer from thyroid lymphoma, poorly differentiated thyroid cancer, or metastasis to the thyroid gland, as the treatment and outcomes are very different. Palliative surgical debulking and tracheostomy should be reserved for patients with airway compromise, as they do not prolong survival. An attempt at a curative resection should be reserved for younger patients, without distant disease, and only when all gross cervical and mediastinal disease can be resected without excessive morbidity. In this select subgroup of patients, curative-intent surgery combined with adjuvant external beam radiation and/or chemotherapy has been shown to prolong survival compared to patients treated with adjuvant therapy alone. Recent studies have shown promising results with the use of combined tyrosine kinase inhibitors, dabrafenib, and trametinib.

11. When is surgery indicated for recurrent thyroid cancer?

Suspected recurrent disease in the neck should be evaluated by FNA. Confirmed nodal recurrence should be treated with a formal dissection of the involved neck compartment. A recurrence in a neck compartment that has already been subjected to formal neck dissection can be challenging due to scarring of the tissue planes, which renders repeat formal neck dissection virtually impossible. In these situations, the risks and benefits of additional surgery must be carefully considered, as the risk of complication increases and the likelihood of cure decreases with each subsequent surgery for recurrence. Observation may be the best option for patients with low-volume, indolent disease. When indicated, focused resection of palpable nodal recurrences can be performed. If not palpable, intraoperative ultrasound can be used to guide the excision. For patients who are poor surgical candidates or have had multiple neck operations, percutaneous ablation with ethanol injection or radiofrequency ablation of nodal metastases is an alternative. Radioiodine is the standard therapy for distant metastatic disease, but isolated metastases can occasionally be surgically resected or treated with external beam radiation.

12. How many times should a thyroid cyst be aspirated if it reaccumulates fluid?

Purely cystic nodules are most often benign, and fine-needle biopsy is not indicated for diagnosis. Aspiration may be performed if a cyst is large and symptomatic. If aspirated, the cyst fluid should be sent for cytology. Recurrence of thyroid cysts occurs in over 50%, and some studies have shown that aspiration followed by ethanol injection has a higher success rate compared to aspiration alone. If the cyst recurs after a second aspiration and is still symptomatic, surgical excision may be considered.

13. List the indications for thyroidectomy in hyperthyroidism.

In the United States, thyroidectomy is not commonly performed for hyperthyroidism unless secondary to a single hyperfunctioning adenoma or because of a toxic multinodular goiter associated with compressive symptoms or containing a suspicious nodule. Despite the excellent success, low recurrence rate, safety, and more rapid return to a euthyroid state, fewer than 10% of patients with hyperthyroidism undergo thyroidectomy. Possible indications for thyroidectomy in patients with hyperthyroidism include:

- Failure of antithyroid medications
- Large goiter and low iodine uptake
- Compression symptoms such as dysphagia, stridor, or hoarseness
- Nodules suspicious for cancer
- Young children (<5 years)
- Pregnant patient who is difficult to treat medically
- Young female who wants to become pregnant in the near future (<6 months)
- Moderate to severe Graves' ophthalmopathy
- Concomitant primary hyperparathyroidism requiring surgery
- Cosmetic concerns

14. How should patients with hyperthyroidism be prepared for surgery?

The 2016 ATA guidelines recommend that hyperthyroid patients should be treated to render them euthyroid prior to surgery; however, multiple recent studies suggest that thyroidectomy can be performed safely prior to achieving a euthyroid state. If used, antithyroid medications administered for 4 weeks prior to surgery are usually adequate. Because recovery of TSH may lag behind thyroid hormone levels, T4 and T3 should be used to determine the adequacy of antithyroid therapy. Some surgeons use potassium iodide (SSKI or Lugol's solution, 3–5 drops three times a day) for 10 days prior to surgery to decrease the vascularity of the goiter and reduce the risk of bleeding. Patients who are very symptomatic may benefit from preoperative beta-blockade. For more rapid induction of a euthyroid state, patients may also be given corticosteroids. In cases of severe, refractory hyperthyroidism, plasmapheresis may occasionally be indicated.

15. What is the effect of thyroidectomy on Graves' ophthalmopathy compared to other treatment modalities?

Ophthalmopathy occurs in about one-third of Graves' disease patients with 5% having moderate to severe eye disease. For those without or with only mild Graves' eye disease, the outcome of the eye disease is felt to be equivalent among different treatment modalities. For patients with mild Graves's eye disease being treated with radioiodine, concurrent use of glucocorticoids is recommended to decrease the risk of worsening the eye disease. Due to the transient increase in TSH receptor antibody levels that occurs following radioiodine therapy and the concern for this worsening Graves' ophthalmopathy, thyroidectomy is recommended for patients with active or moderate to severe Graves' ophthalmopathy.

16. What are the complications of thyroidectomy?

Thyroidectomy is a safe procedure that is typically performed either as an outpatient procedure or, more commonly, with a single overnight stay. Surgeon experience is strongly associated with outcomes. The incidence rates of specific complications after thyroidectomy performed by an experienced thyroid surgeon include:

- Cervical hematoma: 1%
- Permanent/severe hoarseness (i.e., recurrent laryngeal nerve injury): 1%

- Mild/temporary hoarseness: 10%
- Temporary hypocalcemia: 10–15%
- Permanent hypoparathyroidism: 1–3%
- Mortality: <0.1%

17. What is the significance of a "hot" thyroid nodule incidentally discovered on a positron emission tomography (PET) scan?

Fluorodeoxyglucose (FDG) whole-body PET scan is commonly used in the evaluation and surveillance of patients with various types of cancer. A focal area of increased FDG uptake within the thyroid is incidentally noted in up to 4% of PET scans. The risk of malignancy in these lesions is about 33%. Thus, thyroid incidentalomas noted on PET scans have a high risk of malignancy and warrant appropriate diagnostic evaluation. Diffuse FDG uptake is usually related to underlying thyroiditis and in most cases is not indicative of malignancy.

18. What is the appropriate therapy for an intrathoracic (substernal) goiter?

Intrathoracic goiters are typically cervical goiters with mediastinal extension. While commonly asymptomatic, up to 40% of patients present with compressive symptoms resulting from impingement on the esophagus, airway, vascular structures, or nerves. There is general agreement that medical therapy (thyroid hormone suppression and/or radioiodine) is ineffective for intrathoracic goiters. Controversy exists as to whether there is an increased risk of unexpected malignancy in intrathoracic compared to cervical goiters; however, when cases of incidental microcarcinoma are excluded, there does not appear to be an increased risk of malignancy in intrathoracic goiters. Despite this, the presence of an intrathoracic goiter is considered by many as an indication of thyroidectomy. Since the arterial supply of intrathoracic goiters originates in the neck, the vast majority of these tumors can be resected through a cervical approach. Extension into the posterior mediastinum, malignancy, or compression of the vena cava may necessitate a combined cervical and sternotomy approach, although this is required in <5% of cases.

19. When should thyroglossal duct cysts be removed? Describe the operation.

During the embryologic development of the thyroid, a diverticulum forms from the foramen cecum at the base of the tongue and descends as the thyroglossal duct to the future anatomical position of the thyroid overlying the anterolateral surface of the upper tracheal rings. The thyroglossal duct normally disappears during further development but in rare cases will persist as a patent duct or as a thyroglossal duct cyst. Patients may complain of infection, pain, or compressive symptoms, or may have cosmetic concerns. Because of the risk of infection, thyroglossal duct cysts should be removed; this requires excision of the entire cyst and cyst tract from the origin at the foramen cecum down to the cyst itself. Since the tract nearly always passes through the hyoid bone, the center of the hyoid should be resected to lower the risk of recurrence; this causes no disability and requires no repair.

20. How is postthyroidectomy hypocalcemia managed?

Temporary hypoparathyroidism leading to symptomatic hypocalcemia occurs commonly (10–20%) after thyroidectomy. Most postoperative hypocalcemia is mild, temporary, and can be managed on an outpatient basis. It is important to note that parathyroid hormone (PTH) is required for activation of vitamin D, so active vitamin D (vitamin D 1,25, calcitriol) may be required to allow adequate absorption of the calcium until the PTH level recovers. Strategies for prevention and management of post-thyroidectomy hypocalcemia are surgeon and institution specific but should be protocolized. Some recommend that all patients undergoing thyroidectomy receive empiric/prophylactic oral calcium ± calcitriol; however, a common approach is to use the PTH level measured in the recovery room to guide management. In our institution, low-risk patients (PTH >20 pg/ml) require no treatment, high-risk patients (PTH <10 pg/ml) receive both calcium and calcitriol, and intermediate patients (PTH 10–20 pg/ml) receive only calcium. For more severe hypocalcemia, inpatient management for intravenous calcium repletion may be necessary. Permanent hypoparathyroidism occurs in less than 5% of patients following thyroidectomy and can be managed successfully in most patients with oral calcium and calcitriol; however, synthetic parathyroid hormone may be needed if available.

21. Are ultrasound-guided ablative techniques safe and effective for thyroid nodules? What about thyroid cancer?

Ultrasound-guided ablation is an alternative treatment modality for thyroid nodules, which is gaining in popularity and availability. There are multiple different types of energy devices available, but the most common technique, radiofrequency ablation (RFA), uses a percutaneous probe inserted into the nodule by ultrasound guidance to deliver radio waves to generate heat resulting in the destruction of tumor cells and reduction in the size of the thyroid nodule without the need for surgery. Multiple studies have shown this modality to be safe (equivalent or lower risk of hoarseness or other complications compared to surgery) and effective (80% reduction in nodule volume). It does not typically result in complete regression of the nodule, and large nodules may require multiple treatments. Currently, the ATA does not recommend using RFA to treat thyroid cancer; however, there are new studies emerging demonstrating the effectiveness of using RFA to treat micropapillary thyroid carcinomas (<1 cm). This modality could be used as a bridge between active surveillance and definitive surgery.

22. When is active surveillance (or delayed therapy) appropriate for papillary thyroid cancer?

Active surveillance (AS) was first described in Japan as an alternative for patients with very low-risk papillary thyroid cancer. Long-term follow-up from that country and additional studies in the United States have confirmed that the risk of disease progression (tumor growth or new nodal metastases) is low (<10%) and that delaying surgery until disease progression is safe and has equivalent outcomes to immediate surgery at the time of diagnosis. Currently, active surveillance is considered a reasonable and safe alternative to surgery in patients with low-risk tumors (size <1.5 cm without local invasion/proximity to recurrent laryngeal nerve, trachea, or esophagus; no evidence of nodal or distant metastases; and no features of aggressive disease on cytology). The exact size cutoff and criteria for active surveillance are evolving, and other patient-specific factors should be considered such as high surgical risk, short life expectancy, or concurrent medical or surgical issues needing to be addressed prior to thyroid surgery.

23. Is thyroid hormone replacement/supplementation required following hemithyroidectomy?

Most patients do not require thyroid hormone replacement immediately following hemithyroidectomy; however, approximately 40% will eventually require thyroid hormone supplementation. This number increases if the surgery is done for thyroid cancer, since these patients may need TSH suppression. A preoperative TSH level >2.1 mU/L has been shown in some studies to predict a higher likelihood of needing thyroid hormone supplementation.

PARATHYROID

24. Which patients with primary hyperparathyroidism should undergo parathyroidectomy?

All patients with primary hyperparathyroidism (HPT) and "classic" symptoms attributable to the disease (e.g., kidney stones, severe bone disease/fragility fractures, overt neuromuscular syndrome) should undergo surgical intervention; however, most patients do not have these classic symptoms. The most recent international guidelines to assist clinicians in determining which patients with "asymptomatic" HPT should undergo surgery are below. If the patient meets any one of the criteria, then surgery is recommended:

- Age <50 years
- Serum calcium level >1 mg/dL above normal
- Bone mineral density reduced by>2.5 standard deviations below the mean peak adult value (T score)
- Impaired renal function (glomerular filtration rate <60 mL/minute)
- Severe hypercalciuria (24-hour urine calcium >250 mg/24 hr (women), >300 mg/24 hr (men)
- Silent nephrolithiasis on X-ray, ultrasound, or CT
- Silent vertebral fractures on spine X-ray/CT/MRI
- Patients unwilling or unable to undergo surveillance

If the patient does not meet any of the criteria, then *either* surgery *or* continued surveillance are reasonable and safe options.

25. Should subjective symptoms such as fatigue, irritability, and difficulty concentrating be considered indications for surgery in primary hyperparathyroidism?

While only a minority of patients with primary HPT manifest the *classic* symptoms, as many as 90% of patients experience more subtle, subjective symptoms such as fatigue, weakness, musculoskeletal pains, abdominal discomfort, depression, anxiety, irritability, or memory/cognitive difficulties. In fact, some have argued that there is no such thing as truly "asymptomatic" primary HPT! While some studies have shown that patients undergoing parathyroidectomy have an improvement in these subjective symptoms, the results are inconsistent, and it is not possible to predict in any one patient whether these symptoms will improve following surgery. Similarly, some studies have found primary HPT to be associated with an increased risk of cardiovascular disease and early mortality; however, the results of studies investigating whether parathyroidectomy reduces these risks have been conflicting. In contrast to the NIH guidelines, the American Association of Endocrine Surgeons (AAES) guidelines include neurocognitive and/or neuropsychiatric symptoms as an indication for surgery and recommend that a history of cardiovascular disease as well as other nontraditional symptoms be considered in the decision for parathyroidectomy.

26. When should preoperative parathyroid localization studies be performed?

An experienced parathyroid surgeon does not require preoperative localization prior to an initial bilateral neck exploration and will have a surgical success rate of >95%. However, about 85% of patients with primary HPT have a single parathyroid adenoma, so preoperative imaging is commonly performed. If an adenoma is localized, then a focused (a.k.a., minimally invasive) parathyroidectomy can be performed. Ultrasound, 99m technetium sestamibi scan, and high-resolution CT with intravenous contrast, commonly referred to as a 4-D CT, are the most common imaging modalities. The advantages of ultrasound are its low cost, lack of ionizing radiation, and ability to evaluate for concomitant thyroid pathology; however, it is not able to assess for ectopic mediastinal adenomas. Sestamibi and CT scans are costlier and entail radiation exposure but may have improved sensitivity compared to ultrasound. Centers vary as to which modality is used preferentially. Patients with a prior history of neck surgery and certainly all patients with persistent or recurrent hyperparathyroidism should undergo preoperative localization studies prior to planned reexploration. Parathyroid venous sampling with or without arteriography is a highly specialized study performed by interventional radiology that may be useful in select situations of persistent or recurrent hyperparathyroidism when all other modalities have failed to localize the abnormal gland.

27. What is the best treatment for a 45-year-old female with primary hyperparathyroidism but negative preoperative localization studies?

Surgery! The patient's age of less than 50 warrants parathyroidectomy. Remember, failure to localize an abnormal parathyroid on imaging has nothing to do with whether or not a patient *has* HPT or whether or not the patient should undergo surgery. The sensitivity of preoperative localization studies is not perfect, and they fail to localize an abnormal parathyroid approximately 15% of the time. Though multiglandular disease is more common when preoperative localization studies are negative, most patients with negative localization will still turn out to have a single adenoma. The success rate of surgery, if performed by an experienced surgeon, is still high (>95%) when preoperative localization is negative.

28. Define minimally invasive parathyroidectomy.

A conventional parathyroidectomy entails bilateral neck exploration, identification of all four glands, and removal of the grossly enlarged gland(s). The development of accurate preoperative localization studies and a rapid intraoperative parathyroid hormone (ioPTH) assay has fostered the development of minimally invasive approaches to parathyroidectomy. A focused unilateral approach utilizes preoperative imaging to limit the dissection to one side. The abnormal gland is found and removed, and after 10–15 minutes a postexcision blood sample is drawn and the PTH level is compared to a preexcision blood sample. A reduction of the PTH to 50% of the preoperative level and into the normal range predicts successful removal of all hyperfunctioning glands, and the surgery is terminated. If the PTH does not drop appropriately, then all four glands must be identified, as the patient likely has multiglandular disease.

29. What's a MIRP?

Minimally invasive radioguided parathyroidectomy (MIRP) is a second alternative to conventional parathyroidectomy and involves a 99m technetium sestamibi scan the morning of the surgery. An incision is made and either a unilateral or bilateral neck exploration is performed and abnormal parathyroid(s) are removed. A small handheld gamma probe is then used to measure the *ex vivo* radioactive counts of the excised parathyroid to determine whether the gland is hyperfunctioning. If the radioactive counts of the excised parathyroid are 20% or higher compared to the counts in the operative bed, then the gland is presumed to be an adenoma. Contrary to common perception, the gamma probe is not typically used to *localize* the abnormal parathyroid. This is because the thyroid gland also takes up sestamibi, so the high radioactive counts of the thyroid may obscure the ability to use the probe to discern the location of the parathyroid. While this technique can be useful in confirming that an excised parathyroid is hyperfunctioning, it does not rule out the possibility of additional hyperfunctioning glands. Either all four parathyroids must be evaluated or an intraoperative PTH assay should be used to exclude the possibility of multiglandular disease (15%).

30. Summarize the advantages of minimally invasive approaches.

Multiple studies have shown the minimally invasive approaches to be as safe and effective as conventional parathyroidectomy. However, there are also multiple studies showing that a conventional parathyroidectomy (bilateral neck exploration) can similarly be performed through a small incision, on an outpatient basis and with excellent results. Some studies have found the minimally invasive approaches to be more time- and cost-efficient because they limit the amount of dissection required. Since the minimally invasive approach is typically performed through a slightly smaller incision, cosmesis may be improved.

31. How is the ioPTH assay utilized in parathyroid surgery?

The half-life of PTH is 3–5 minutes, which allows for a rapid assay for ioPTH to be used intraoperatively to assess the functional success of the operation. This test is performed by drawing a sample of blood before the operation and 10 minutes after the suspected abnormal gland(s) has/have been removed. A reduction of the ioPTH by 50% predicts successful removal of all hyperfunctioning glands, and the surgery is terminated. The rate of multiglandular disease is approximately 15% when ioPTH is used to determine the completeness of resection, whereas the rate is 10–35% when conventional parathyroidectomy is performed (i.e., bilateral neck exploration and removal of grossly enlarged parathyroids). Therefore, the use of ioPTH may prevent the unnecessary removal of glands that *appear* slightly enlarged but are not functional.

32. What is the expected success of surgery for primary hyperparathyroidism?

Parathyroidectomy is highly successful for primary hyperparathyroidism, correcting hypercalcemia in more than 95% of patients when performed by an experienced surgeon. Bone density stabilizes or increases in the vast majority of patients. Successful parathyroidectomy significantly decreases the risk of kidney stone recurrence. Following successful surgery, many patients experience improvement in the vague nonspecific symptoms of hyperparathyroidism.

33. Describe the appropriate management of a "missing" parathyroid.

Despite meticulous operative techniques during conventional parathyroidectomy (identification of all four glands), the surgeon occasionally encounters a "missing gland." Up to 20% of parathyroid glands are ectopic with the most common locations being within the thymus, retroesophageal, and intrathyroidal. A systematic search of the most common ectopic locations is required for successful outcomes in these patients. When three normal glands have been identified and the fourth gland is not in a normal position, the most likely ectopic location depends on whether it is a missing upper or lower gland.

34. List the likely locations for an ectopic inferior parathyroid gland.

- Thyrothymic ligament
- Thymus

- Mediastinum outside thymus
- Undescended gland

35. List the likely locations for an ectopic superior parathyroid gland.

- Retroesophageal
- Tracheoesophageal groove
- Posterosuperior mediastinum
- Carotid sheath
- Intrathyroidal

36. What is the correct surgery if a patient has multiglandular parathyroid disease?

A single adenoma is by far the most common cause of primary hyperparathyroidism (85%). Depending on the method used to define multiglandular disease (i.e., intraoperative PTH assay versus gross appearance/size), the reported rates range from 15–35%. The multiglandular disease can be due to either multiple adenomas or four-gland hyperplasia. Hyperplasia may be sporadic or secondary to a genetic predisposition such as multiple endocrine neoplasia (MEN) syndrome. When all four glands are hyperplastic, a subtotal parathyroidectomy is required (removal of 3.5 glands). It is important that the surgeon be careful to preserve the blood supply to the parathyroid remnant. If after removing half the final parathyroid the remnant appears ischemic, then it should be excised and auto-transplanted, either to the brachioradialis muscle in the nondominant forearm or the sternocleidomastoid muscle. Postoperatively, most patients (95%) will have normal calcium and low or normal PTH levels; however, permanent hypoparathyroidism occurs in 2–3% and recurrent hyperparathyroidism occurs in about 10% of patients.

37. What are the indications for surgery for secondary/tertiary hyperparathyroidism?

While all patients with dialysis-dependent renal failure develop secondary hyperparathyroidism, only a minority of patients develop tertiary hyperparathyroidism, which occurs when somatic mutations occur within one or more of the hyperplastic parathyroids resulting in adenomatous transformation. Medical management with phosphate binders, active vitamin D analogs (calcitriol), and calcimimetics (cinacalcet) will keep the PTH, calcium, and phosphate levels under control in most patients. Most experts agree that parathyroidectomy is indicated for patients who, despite optimal medical management, have refractory hyperparathyroidism (no absolute value but PTH >600–800 pg/ml commonly cited) and significant associated signs and symptoms. The most common signs and symptoms include: hypercalcemia with hyperphosphatemia (calcium x phosphate product >50), bone and joint pain and/or fractures, proximal muscle weakness, extra skeletal calcification and/or calciphylaxis, and pruritus. Indications for parathyroidectomy in asymptomatic patients with refractory hyperparathyroidism are more controversial, but some recommend it for patients with PTH >1000 pg/mL who are younger (<65 years) and without other significant comorbidities.

38. Discuss the advantages and disadvantages of subtotal parathyroidectomy (SPTx) versus total parathyroidectomy with autotransplantation (TPTx + AT) for refractory secondary/tertiary hyperparathyroidism.

There is no significant difference in persistent/recurrent HPT or the rate of permanent hypoparathyroidism between SPTx and TPTx + AT. The advantage of TPTx + AT is that persistent or recurrent hypercalcemia can be treated by partially or completely removing the grafts (usually placed in a forearm muscle) under local anesthesia, while the same complication occurring after SPTx requires repeat neck operation with higher morbidity.

39. List the complications of parathyroidectomy for primary hyperparathyroidism and their prevalence.

- Persistent hyperparathyroidism: <5%
- Recurrent hyperparathyroidism: 5–10%
- Transient hypocalcemia: 10–25%
- Permanent hypoparathyroidism: 2–5% (<1% for solitary adenoma)
- Temporary recurrent laryngeal nerve injury: 3%
- Permanent recurrent laryngeal nerve injury: <1%
- Mortality: <0.1%

40. Define persistent or recurrent hyperparathyroidism.

Persistent hyperparathyroidism is defined as the failure of calcium and PTH levels to normalize or remain normal in the initial 6 months after the operation, whereas recurrent hyperparathyroidism is defined by the recurrence of hypercalcemia after 6 months.

41. What is the most common cause of an elevated PTH but normal calcium following parathyroidectomy?

The most important lab to check following parathyroidectomy is the serum calcium level because the surgical cure is defined by normal postoperative serum calcium; however, persistent PTH elevation with normal serum calcium can be observed in up to 30% of patients following parathyroidectomy. This can be disconcerting to the patient and surgeon but in most cases is not due to persistent or recurrent HPT. The cause of this phenomenon is likely multifactorial, but vitamin D deficiency, rapid bone turnover (hungry bone syndrome), and inadequate calcium intake are thought to be the main causes. Postoperative supplementation with calcium and vitamin D decreases this phenomenon. Long-term studies have shown that the PTH eventually returns to normal in most patients and that the long-term recurrence rate is only slightly increased in this subset of patients.

42. Discuss the approach to patients with persistent or recurrent hyperparathyroidism.

The approach to patients with persistent or recurrent hyperparathyroidism requires confirmation of the diagnosis (exclude familial hypocalciuric hypercalcemia, vitamin D deficiency, etc.), estimation of disease severity to ensure that reoperation is justified, careful review of the operative and pathology reports, and preoperative localization. If repeat operation is considered necessary, assessing vocal cord function should be considered. Causes of failure include missed adenoma in a normal location, ectopic glands, inadequate resection in multiglandular disease, and supernumerary glands.

43. Discuss the options for treatment of persistent or recurrent hyperparathyroidism.

While preoperative localization is optional prior to an initial surgery for hyperparathyroidism, it is essential in cases of persistent or recurrent disease, as the success rate of the surgery is much higher when the abnormal gland has been accurately localized. Multiple modalities are often utilized with 99m technetium sestamibi scan, ultrasound and CT scan being the most common. Having a correlation of the location of the abnormal gland on two different imaging modalities is very reassuring and is used by some surgeons as a criterion for reoperation in persistent hyperparathyroidism. Repeat cervical exploration is successful in normalizing PTH levels in about 85% of patients and may be aided by intraoperative ultrasound and ioPTH assay. Mediastinal parathyroid tissue is most often removed via the transcervical approach, but thoracoscopy or median sternotomy may be required 1–2% of the time. Angiographic ablation of mediastinal parathyroid tissue using high doses of ionic contrast may be successful in selected patients and prevent sternotomy.

44. How does one recognize parathyroid cancer?

Parathyroid cancer is the rarest of all endocrine tumors, with a reported incidence of <1% in patients with primary hyperparathyroidism. It is difficult to distinguish parathyroid cancer from the more common benign causes of hyperparathyroidism, and the diagnosis is frequently not suspected preoperatively. Parathyroid cancer should be suspected preoperatively when patients present with rapid onset, severe, symptomatic hypercalcemia (>14 mg/dL), very high PTH levels (>5 times normal), a palpable neck mass, or hoarseness. It should be suspected intraoperatively when the tumor is large, firm, fibrotic, or invasive to the thyroid or other surrounding structures. A successful outcome requires early recognition and complete resection of the tumor and any involved structures.

45. Describe the management of parathyroid cancer.

Surgery is the mainstay of treatment for parathyroid cancer, as radiation and chemotherapy have shown little benefit. Local invasion and pathologic nodes should be assumed to represent cancer. Any suspicious parathyroid lesions should be carefully removed without disrupting the parathyroid capsule, as this may result in tumor spillage and local recurrence. If a parathyroid gland is obviously abnormal and infiltrating other tissues, those tissues should be resected en bloc with the tumor whenever possible, including the ipsilateral thyroid lobe when necessary. Removal of the central nodes on the side of the tumor is indicated at the initial operation. Any obviously enlarged lateral nodes should be resected by formal neck dissection. Prophylactic neck dissections have shown no benefit. The histopathologic diagnosis of this cancer is also difficult, thus an intraoperative frozen section is rarely useful other than to confirm parathyroid tissue.

46. Give the recurrence and survival rates for parathyroid cancer.

Recurrence rates are high and depend on whether the patient underwent a routine parathyroidectomy for presumed benign disease (>50% recurrence) or an en bloc resection for suspicion of cancer (10–33%). Despite this high recurrence rate, prolonged survival is still possible. The National Cancer Database reports 5- and 10-year survival rates of 85.5% and 49.1%, respectively.

47. What is normocalcemic primary hyperparathyroidism? Are treatment and outcomes the same as for classic, hypercalcemic primary hyperparathyroidism?

Normocalcemic primary hyperparathyroidism (NPHPT) is a recognized variant of primary hyperparathyroidism (PHPT), characterized by normal total and ionized serum calcium concentrations and elevated parathyroid hormone (PTH) levels. It is a diagnosis of exclusion, and all secondary causes for hyperparathyroidism (renal failure, vitamin D deficiency, inadequate calcium intake or malabsorption, urinary calcium wasting) must be ruled out. Surgery for NPHPT is somewhat controversial, as these patients are more likely to have multiglandular disease and to require subtotal parathyroidectomy and, despite this, have a higher rate of persistent hyperparathyroidism than patients with classic hypercalcemic PHPT. In contrast to classic hypercalcemic PHPT, some surgeons use preoperative imaging in the decision on whether to operate on NPHPT patients and reserve surgery for only those whose imaging localizes an abnormal gland. There is conflicting data as to whether patients undergoing surgery for NPHPT derive the same benefit in terms of improvement in bone density as do patients with classic PHPT and more studies are needed to evaluate the long-term outcomes for these patients.

KEY POINTS

Thyroid Surgery

- Active surveillance may be appropriate for low-risk papillary thyroid cancer less than 1–1.5 cm with no invasion or evidence of nodal/distant metastases.
- Thyroidectomy is indicated for tumors over 4 cm or those with extrathyroidal extension or nodal/distant metastases, while *either* thyroidectomy *or* lobectomy may be appropriate in the absence of those features.
- Lymph node involvement in thyroid cancer should be treated with a systematic compartment node dissection.
- Incidental FDG avid thyroid nodules discovered on PET scans have a 33% risk of malignancy and should be evaluated by ultrasound-guided FNA.

Parathyroid Surgery

- Indications for parathyroidectomy in primary hyperparathyroidism include the classic symptoms of nephrolithiasis, severe bone disease/fragility fractures, and overt neuromuscular syndrome.
- Indications in asymptomatic patients include high serum calcium (>1.0 mg/dL above normal), age under 50 years, osteoporosis, reduced creatinine clearance, or significant hypercalciuria.
- Surgery for primary hyperparathyroidism results in normocalcemia in greater than 95% of patients when performed by an experienced parathyroid surgeon.
- Parathyroid cancer is rare but should be suspected in patients with a palpable mass and symptomatic hypercalcemia that is severe and of rapid onset.

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CHAPTER 66

Adrenal Surgery

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1. What is the arterial and venous anatomy of the adrenal gland?

The two adrenal glands are located in the retroperitoneum superior to the kidneys.

The arterial blood supply consists of three arteries: the superior adrenal artery, which is a branch of the inferior phrenic artery; the middle adrenal artery, a direct branch from the abdominal aorta; and the inferior adrenal artery, a branch of the renal artery. The adrenal glands generally have a single central vein. The main central vein on the right exits the upper one-third of the gland and drains directly to the inferior vena cava. The left central vein is longer and drains to the left renal vein. However, up to 13% of patients may have variant venous anatomy. These variants can include smaller accessory veins in addition to or replacing the main central vein, more than one central vein, the left central vein draining into the inferior phrenic vein, and the right central vein draining into a hepatic vein.

2. Should all incidentally discovered adrenal masses be resected?

No. Incidentally discovered and clinically occult adrenal masses, colloquially known as incidentalomas, are common (about 5% in modern imaging series) due to the increasing ubiquity of abdominal imaging. Most incidentalomas are nonfunctional and benign (70–80% cortical adenomas), requiring only surveillance. The indications for adrenalectomy: tumors >4 cm, functional tumors, tumors with imaging characteristics concerning adrenocortical carcinoma (ACC), and select patients with cancer metastases to the adrenal gland. The risk of ACC is directly related to tumor size: 2% for 4 cm or less, 6% for 4–6 cm, and 25% for greater than 6 cm.

3. A patient with right lower quadrant pain underwent an abdominal CT scan with IV contrast in the Emergency Department; a 2-cm left adrenal nodule was noted. What is the next step?

When evaluating a patient with an adrenal incidentaloma, a provider should “AIM” to answer these three questions:

- **A**ctive: Is the tumor hormonally hyperactive?
- **I**maging: Does the lesion have imaging features concerning ACC (size >4 cm, irregular borders, invasion to surrounding tissue, greater than 10 Hounsfield Units on unenhanced CT)
- **M**etastatic deposit: Does the patient have a history of prior nonadrenal malignancy, indicating that the lesion may be a metastatic deposit?

The workup to answer these questions begins with a thorough history, including symptoms of hyperactive adrenal lesions and past medical history (query latest colonoscopy, mammography, and CXR or surveillance CT scan for smokers; prior personal history of malignancy including skin cancer, especially melanoma; and family history of malignancy), and physical exam. The patient should undergo biochemical testing to assess for tumor hyperfunctionality. The adrenal nodule should be evaluated with a dedicated adrenal protocol CT scan to determine Hounsfield Units on unenhanced CT and IV contrast washout characteristics. If the adrenal nodule is <4 cm, the patient may follow up with a repeat adrenal contrast-enhanced CT scan in 12 months. Once the tumor is stable on two CT scans over 12 months, no further imaging is necessary. If the biochemical tests are negative, there is no strong evidence for continued biochemical surveillance. However, yearly evaluations with the patient’s primary care physician and continued surveillance for comorbidities related to hyperfunctional adrenal lesions such as diabetes and hypertension should be continued. Repeated biochemical testing should be completed if comorbidities worsen or newly developed. The risk of a nonfunctional adrenal tumor developing overt hyperfunctionality is very low, 0.3% over an average follow-up of 50 months.

4. What is the initial laboratory workup of an adrenal mass?

Up to 20% of adrenal incidentalomas may be biochemically hyperfunctional and should be resected. Therefore, patients should be screened for hypercortisolism, pheochromocytoma, and hyperaldosteronism. The evaluation for hyperaldosteronism is reserved for patients with hypertension with or without hypokalemia. The initial lab work includes:

- 1-mg overnight dexamethasone suppression test (DST): suggestive of a cortisol-producing tumor if morning cortisol >5 μg/dL and deemed nonfunctional if cortisol <1.8 μg/dL. Cortisol levels between 1.8 and 5 μg/dL are labeled "mild autonomous cortisol secretion" (MACS). In these cases, the 1-mg overnight DST should be repeated to confirm the diagnosis. The DST should not be used in pregnant patients or those taking exogenous estrogen due to the increased rate of false positives. The 24-hour urinary cortisol and bedtime salivary cortisol assays may also be helpful in analyzing the extent of autonomous cortisol secretion to confirm hyperfunctionality or degree of MACS.
- 24-hour urine metanephrines and catecholamines or plasma metanephrines and normetanephrines: diagnostic of pheochromocytoma if greater than two to four fold above the upper limit of normal. Medications and substances including acetaminophen, antidepressant medications such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), some antihypertensive medications, cocaine, amphetamines, and caffeine can result in elevated levels leading to false positives. These medications and substances should be stopped at least 2 weeks prior to testing if possible.
- Plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio (aldosterone to renin ratio, ARR): suggestive of aldosteronoma if PAC >15 ng/dL and ARR >20. ARR is not diagnostic by itself, and confirmatory testing is needed. The two most common confirmatory tests are the oral salt loading test and the normal saline suppression test. The oral salt loading test involves 3 days of a 6000 mg sodium chloride diet or taking 2 g of sodium chloride tablets three times per day for 3 days. A 24-hour urine collection is then performed. Sodium urinary excretion of 4600 mg confirms adequate sodium loading, and urinary excretion of aldosterone >12 mcg is then consistent with hyperaldosteronism. An alternative to this is the normal saline infusion test. The patient receives 2 liters of normal saline intravenously over 4 hours. A subsequent PAC >10 ng/dL is then consistent with hyperaldosteronism.

5. What imaging studies are available for evaluating adrenal pathology?

Computed tomography (CT) scan is the initial modality of choice and normally sufficient for benign adenomas, both nonfunctional and hyperfunctional. If a noncontrast CT scan is consistent with a homogenous, <4 cm mass, and ≤10 Hounsfield Units then no further imaging is immediately required. Adrenal protocol CT consists of thin-cut imaging through the adrenal glands first without intravenous contrast, and then with contrast followed by delayed (usually 10–15 minutes) images to assess contrast washout. This is required for indeterminate tumors not meeting the above criteria. MRI is considered essentially equivalent to CT for adrenal tumors, and is a reasonable, though more expensive, alternative to CT scans. MRI should be considered for patients with contrast allergy and in situations where radiation exposure should be limited (pregnancy and pediatric patients with known germline mutations). MRI is also helpful in evaluating vascular involvement in cases of suspected ACC.

Metaiodobenzylguanidine (MIBG) SPECT/CT scans are classically used to assess pheochromocytomas in recurrent, familial, and syndromic cases. They are also useful in locating extra-adrenal paragangliomas when a biochemical diagnosis is made but no lesion is localized to the adrenal glands. MIBG acts as an analog of norepinephrine and subsequently localizes to cells of neuroendocrine origin. DOTATATE PET/CT scans utilize the somatostatin receptor in neuroendocrine tumors, and recent studies demonstrate improved sensitivity and specificity of DOTATAE scans, allowing for DOTATATE scans to now largely replace MIBG scans for pheochromocytomas and paragangliomas.

As with many other forms of malignancy, FDG PET/CT can be useful to confirm ACC in equivocal cases and to evaluate for metastases both from and to the adrenal glands.

6. What findings on CT help to distinguish between benign and malignant tumors?

Adrenal lesion size and imaging characteristics are two significant predictors of malignancy. ACC accounts for only 2% of lesions when less than 4 cm but up to 25% of those greater than 6 cm. Lesions between 4 and 6 cm have a 6% risk of being malignant. Benign lesions are typically

<4 cm, homogeneous with smooth borders, and have high lipid content (low attenuation, less than 10 Hounsfield units [HU] on noncontrast images) with rapid contrast washout (>50% washout on delayed images). Malignant tumors are typically >6 cm, heterogeneous with irregular borders, and have increased noncontrast attenuation (>10 HU) with slower contrast washout.

7. Should adrenal nodules be evaluated with percutaneous biopsy?

No. Percutaneous biopsy is reserved for those with a history of nonadrenal cancer to evaluate for metastasis to the adrenal gland, but only if the results will alter the treatment plan. Pheochromocytoma must be excluded with biochemical testing prior to biopsy to avoid potentially precipitating a hypertensive crisis. Percutaneous biopsy cannot differentiate an adrenal adenoma from an ACC and increases the risk of local recurrence of ACC following resection due to tumor capsule violation and seeding. Therefore, biopsies of the adrenal gland are rarely done as FDG PET/CT scans can more readily and noninvasively diagnose metastatic lesions of the adrenal glands.

8. Is adrenalectomy best performed with an open or laparoscopic technique?

Laparoscopic adrenalectomy is the approach of choice for benign adrenal tumors except when massive (>8–12 cm). Laparoscopic adrenalectomy has been associated with decreased hospital stay, less postoperative pain, less blood loss, shorter recovery, and overall increased patient satisfaction compared with the open techniques. Open adrenalectomy and conversion from laparoscopic to open is the gold-standard procedure when malignancy is suspected. However, recent studies have shown that laparoscopic resection of malignant tumors may be appropriate for smaller tumors without evidence of local invasion when done at specialized centers by experienced surgeons.

9. What are the possible laparoscopic approaches for adrenalectomy?

The laparoscopic approaches for adrenalectomy are anterolateral, supine, and retroperitoneoscopic. The anterolateral laparoscopic transabdominal approach is a common technique in which the patient is positioned in a lateral decubitus position with the side of the lesion up. The anterolateral approach provides excellent unilateral exposure. The supine anterior transabdominal approach allows access to both adrenal glands; however, surgical exposure of the adrenal glands is more challenging due to the liver and spleen, which more directly overlie the adrenal glands in this position. The posterior laparoscopic retroperitoneal (retroperitoneoscopic) approach in the prone position avoids entering the peritoneal cavity and affords access to the bilateral adrenal glands without repositioning. However, it is limited by a smaller working space, thus precluding the removal of larger lesions (>4–7 cm), and it adds complexity for an en bloc resection of lesions suspected to be malignant. The retroperitoneal approach is also more difficult in patients with a large BMI, the classical cutoff for a successful retroperitoneal approach being BMI <35 kg/m^2. While individual randomized controlled trials have had mixed outcomes, results from meta-analyses indicate that the retroperitoneoscopic approach may offer slight advantages with shorter operative time, decreased blood loss, decreased length of stay, and reduced postoperative pain. The retroperitoneoscopic approach may also lead to financial cost savings.

10. What is hyperaldosteronism and when is surgery indicated?

Primary aldosteronism (PA) or primary hyperaldosteronism, also known as Conn’s disease, is a clinical syndrome of refractory hypertension (often requiring at least 3 antihypertensive agents) sometimes combined with spontaneous hypokalemia (serum potassium <3.5 mEq/L) or severe (<3 mEq/L) diuretic-induced hypokalemia. However, only 9–37% of patients initially present with hypokalemia. In the vast majority, PA is due to either bilateral adrenal hyperplasia (60–65%) or an aldosterone-producing adenoma (30–40%). More rare causes include unilateral hyperplasia, ACC, and familial PA (approximately 1–2%). Surgery is only indicated when there is unilateral hypersecretion of aldosterone.

11. What is adrenal vein sampling and when is it indicated?

Adrenal vein sampling (AVS) is the gold-standard test to evaluate for unilateral hypersecretion in PA; AVS has been shown to change management in up to 10–15% of patients compared to using CT/MRI alone. For example, a patient might have bilateral adrenal hyperplasia but also incidentally have a nonfunctional adenoma in one of the adrenal glands. The assumption without AVS is that the adenoma is producing excess aldosterone, but an adrenalectomy would not be indicated for the PA if it is due to bilateral hyperplasia, and instead medical therapy would be appropriate.

AVS is an interventional radiology procedure that uses endovascular catheters to selectively cannulate and sample blood from the right and left adrenal veins and the inferior vena cava (IVC). Typically, AVS is done before and after the administration of cosyntropin (ACTH) to optimize and control hormone secretion. Aldosterone and cortisol levels are measured in blood samples obtained from the right and left adrenal veins and IVC and these values are used to calculate three indices to determine if there is unilateral hypersecretion: the selectivity index (SI), the lateralization index (LI), and the contralateral suppression index (CSI). The SI is calculated by dividing each adrenal cortisol level by the IVC cortisol level, indicating proper cannulation. Cutoff values of >2 and >5 are typically used for nonstimulated and cosyntropin-stimulated tests, respectively. The LI index is calculated by dividing the dominant adrenal aldosterone corrected to cortisol level by the contralateral adrenal aldosterone corrected to cortisol level. A ratio of >4 is indicative of unilateral disease. The CSI is calculated by dividing the nondominant adrenal aldosterone corrected to cortisol level by the IVC aldosterone corrected to cortisol level and indicates that the contralateral adrenal aldosterone production is suppressed in response to the excess of aldosterone produced by the dominant adrenal. A CSI <1 confirms lateralization to the side of suspected dominant secretion.

12. Do all patients with hyperaldosteronism require adrenal vein sampling prior to surgery?

AVS may be omitted in younger patients (<35 years old) with a clear adenoma on CT and confirmed biochemical diagnosis of profound PA, as they are less likely to have other confounding adrenal nodules or bilateral disease. This confers an approximate 3% risk of wrong-side adrenalectomy and a 2% risk of inappropriate adrenalectomy for bilateral disease. The option to omit AVS is especially true in regions where AVS is not readily available, and the age limit may be raised to <45 years old. Additionally, AVS should not be used for a patient with other indications for surgery, such as adenoma >4 cm and imaging characteristics concerning ACC.

13. Describe the appropriate perioperative management of pheochromocytoma.

Surgical resection is the only chance for cure for patients with pheochromocytoma. All patients with the biochemical diagnosis of pheochromocytoma should undergo preoperative alpha-adrenergic blockade for 7–14 days leading up to surgery in order to decrease the likelihood of severe hypertension during the manipulation of the tumor. Classically, phenoxybenzamine, a nonselective long-acting alpha-adrenergic blocker, was used; however, the current standard of care is to use short-acting alpha-adrenergic blockers, such as prazosin, doxazosin, and terazosin. Calcium channel blockers (nicardipine) are an alternative option. A preoperative beta-adrenergic receptor blocker is indicated for tachyarrhythmias only after the administration of alpha-adrenergic blockade. Propranolol (10–40 mg every 6–8 hours) is the most commonly used beta-blocker in this scenario. The goals of treatment are a BP <130/80 seated and more than 90 systolic blood pressure when standing as well as a heart rate of 60–70 seated and 70–80 standing. Patients should increase their fluid and salt intake (>5 grams/day) after starting alpha-blockers to attain fluid expansion because patients with pheochromocytomas typically have intravascular volume depletion.

Chromogranin A (CgA) is a nonspecific marker of neuroendocrine tumors, elevated in 91% of patients with pheochromocytoma. CgA is used as a marker for monitoring disease following resection, and a baseline level should be checked before adrenalectomy.

14. When is genetic testing indicated for pheochromocytoma?

Genetic testing is recommended for all patients with pheochromocytoma, as 35–40% of cases are hereditary. Examples of an inherited predisposition to pheochromocytomas and paragangliomas include MEN2A, MEN2B, von Hippel-Lindau Syndrome, neurofibromatosis, and familial paraganglioma. Familial paraganglioma will often be due to mutations encoding succinate dehydrogenase (SDH). Mutations of succinate dehydrogenase subunit B (SDHB) encompass up to 43% of malignant disease cases; 37% of patients with a SDHB mutation will ultimately have metastatic disease.

15. What percentage of pheochromocytomas are malignant?

Unfortunately, there is no reliable histological basis to distinguish benign from malignant pheochromocytomas and paragangliomas. Metastasis is the single defining characteristic of malignancy. Therefore, lifelong annual biochemical testing to assess for recurrent or metastatic disease is recommended because about 10% of pheochromocytomas are malignant and up to 50% of extra-adrenal paragangliomas are malignant.

16. What is a cortical-sparing adrenalectomy and when is it indicated?

Hereditary pheochromocytomas have an increased risk for bilateral and recurrent pheochromocytoma. Patients with hereditary pheochromocytomas may undergo a cortical-sparing (partial) adrenalectomy to prevent adrenal insufficiency should another pheochromocytoma arise, requiring additional adrenalectomy on the contralateral side. This approach balances the benefit of avoiding the need for lifelong hormone replacement due to adrenal insufficiency (23% risk with cortical sparing versus 100% with bilateral total adrenalectomy) with a low risk of recurrence in the adrenal remnant following cortical-sparing adrenalectomy (13%).

17. Describe the appropriate perioperative management of a patient with a cortisol-secreting adrenal adenoma.

Diabetes and hypertension should be adequately treated prior to surgery. Patients with Cushing's syndrome have an increased relative risk for thromboembolic complications due to increased clotting factors (fibrinogen and von Willebrand Factor) and a relative hypofibrinolytic state; measures to prevent this complication should be implemented.

Intraoperative glucocorticoid replacement is necessary for patients with overt Cushing syndrome but normally is not needed for patients with mild autonomous cortisol secretion (MACS). The normal dosing for overt Cushing syndrome is 50–100 mg IV hydrocortisone prior to incision followed by 25–50 mg of IV hydrocortisone every 8 hours for 24 hours then followed by a rapid taper of oral prednisone to a final dose of 10 mg daily. This supplemental glucocorticoid may be needed for several months to a few years while the hypothalamic-pituitary-adrenal (HPA) axis recovers following its suppression due to the cortisol-secreting adenoma. Ultimately, these patients will need to be followed by an endocrinologist, and therefore an endocrinologist should be consulted during the hospitalization to tailor the glucocorticoid replacement plan.

Up to 48% of all incidentalomas and 13–33% of aldosteronomas will have comorbid MACS, and MACS is linearly associated with mortality. Therefore, patients with MACS will need to be evaluated following surgery to determine if they too need supplemental glucocorticoids. No glucocorticoids should be given by anesthesia on the day of surgery. The morning cortisol level is then checked at 8 A.M. on postoperative day one. If it is >10 mcg/dL, the patient may be discharged without supplemental therapy. If it is <10 mcg/dL, a cosyntropin stimulation test will need to be completed. 250 mcg of cosyntropin (ACTH) is given IV, and cortisol levels are checked at 30 and 60 minutes. If the cortisol level reaches 18 mcg/dL or greater, they may be discharged without supplementation. The time for the HPA axis to recover after adrenalectomy for MACS varies from weeks to months. Cosyntropin stimulation studies can be used to determine when steroids can be discontinued.

18. If a patient undergoes adrenalectomy for lateralized primary aldosteronism, do they need their cortisol levels checked postoperatively?

Thirty-seven percent of patients undergoing unilateral adrenalectomy for noncortisol-secreting tumors develop hypocortisolemia. Therefore, postunilateral adrenalectomy patients must be evaluated for the need for steroid supplementation to prevent adrenal insufficiency. A DST in the preoperative setting will determine which patients might require steroid supplementation (cortisol hypersecretion or MACS as above). If a DST was not completed in the preoperative period, a cortisol level the morning after surgery will guide the need for steroid supplementation (see question 17).

19. Summarize the long-term success of adrenalectomy for functional tumors.

Patients who undergo adrenalectomy for unilateral hyperaldosteronism can expect a nearly 100% cure rate of hypokalemia, and 84% of patients will have an improvement in hypertension, with

37% having complete resolution and 47% having a reduction in the number or dose of antihypertensive medications. 94% of patients will have normalization of their aldosterone renin ratio (ARR). The aldosterone resolution score (ARS) roughly predicts the chances of complete resolution of hypertension. The factors that indicate a favorable outcome are: 2 or fewer antihypertensive agents preoperatively, BMI ≤25 kg/m^2, duration of hypertension <6 years, and female sex. Other factors that have been found to predict favorable outcomes include age <40 years, good response to spironolactone, absence of diabetes, and higher ARR. In older patients with severe, long-standing hypertension associated with renal dysfunction, adrenalectomy may not normalize blood pressure but usually results in easier control of hypertension with fewer or lower-dose medications.

Adrenalectomy for nonfamilial, benign pheochromocytomas is curative in most cases. However, a long-term recurrence rate as high as 16.5% has been reported, and therefore patients should undergo lifelong surveillance with annual laboratory testing.

Adrenalectomy results in excellent improvement in the symptoms of Cushing's syndrome and improves patient quality of life. Hypertension and diabetes will resolve in 65–80% of patients. The physical changes of Cushing's syndrome will resolve in 85%. These improvements take 6–18 months to occur. Patients with MACS can similarly expect an improvement in glycemic control and hypertension with 28% and 68% of patients expected to show improvement, respectively.

20. Describe the appropriate management of adrenal malignancy.

ACC is a rare (1 case/million people/year, <5% of all incidentalomas, and 0.2% of all cancer deaths in the United States) but aggressive cancer with a poor prognosis. At the time of diagnosis, approximately 25% of patients will have nodal involvement, and 20% will have distant metastases. About 60% of ACCs are functioning tumors. The mean size of these tumors at the time of diagnosis is >10 cm. Survival is mainly dependent on the stage at diagnosis. Patients undergoing complete resection of stage I tumors have a 5-year survival of 80%, whereas patients with metastases or invasion into other organs (stage IV) have a 13% 5-year survival and median survival of less than 12 months.

The only chance for cure is surgery, which should be offered to all patients without metastases with a reasonable surgical risk. The tumor and surrounding tissue must be resected in an en bloc fashion due to high recurrence rates of up to 80%. Surgery should also be considered for young patients with isolated, easily resectable metastases. All patients should be referred to a multidisciplinary clinic at a specialized center for complete workup and treatment. Patients should have a CT scan of the chest to evaluate for metastases to the lungs. MRI can be complementary to CT scans of the abdomen to better assess for liver metastases and vascular involvement. Nuclear medicine scans can also be beneficial to evaluate for metastases.

Despite limited response rates, patients with stage III or IV disease are frequently offered adjuvant therapy with mitotane (± cytotoxic chemotherapy including etoposide, cisplatin, and doxorubicin) due to the high recurrence rate of locally invasive ACC. Mitotane is an adrenocorticolytic agent indicated for suspected incomplete resection and tumors with a high proliferative rate (Ki67 >10%). Radiotherapy may be used in a palliative fashion for high-risk metastases and symptomatic tumor burden. Targeted molecular therapies and immunotherapies are currently under investigation for ACC.

KEY POINTS

Adrenal Tumors

- **"AIM"** to answer these three questions during the evaluation of an adrenal incidentaloma: Is it **A**ctive? Does it have concerning features on **I**maging? Does it represent a **M**etastatic deposit?
- Adrenal biopsy is rarely indicated given the use of noninvasive FDG PET/CT scans to assess metastases to the adrenal glands, and pheochromocytoma must be ruled out first.
- Alpha blockade for 7–14 days is crucial in patients undergoing adrenalectomy for pheochromocytoma.
- Adrenalectomy is only indicated for unilateral primary hyperaldosteronism. Adrenal vein sampling is considered the gold standard test to confirm unilateral disease and is recommended for most patients.
- Evaluation of the need for steroid supplementation after adrenalectomy should be completed in all patients undergoing unilateral adrenalectomy for noncortisol-secreting tumors.

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Pancreas and Other GI Neuroendocrine Tumors

Alex Harrelson

CHAPTER 67

1. What are PNETs?

Pancreatic neuroendocrine tumors (PNETs) are a group of epithelial neoplasms originating from the endocrine cells of the pancreas (also known as islet cell tumors). They are categorized as either functional or nonfunctional, depending on the tumor's ability to secrete hormones such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), or somatostatin. The majority (50–75%) of PNETs are nonfunctional. Nonfunctional PNETs typically manifest similarly to pancreatic adenocarcinoma with abdominal pain or biliopancreatic duct obstruction and mass effect. They are often diagnosed at advanced stages because of their slow growth pattern leading to a delay in the onset of symptoms. Nonfunctional PNETs are incidentally discovered at an increasing rate as the use of high-quality abdominal imaging becomes more common. Functional PNETs are often diagnosed based on presenting symptoms caused by the overproduction of hormones. PNETs are usually sporadic but approximately 10% can be associated with genetic syndromes: Multiple Endocrine Neoplasia Types I and IV (MEN1, MEN4), von Hippel Lindau (VHL) Syndrome, Neurofibromatosis 1 (NF1), and Tuberous Sclerosis Complex.

2. How common are PNETs?

PNETs are rare with an incidence of ≤1 case per 100,000 individuals per year and constitute only 1–2% of all pancreatic tumors. The incidence in the United States has increased in frequency over the past thirty years due to increased awareness, improvements in diagnostic imaging, and overall increased use of CT scans and MRIs. Most people with PNETs are older with an average age of 60 years at diagnosis. These tumors are slightly more common in men than women. Autopsy series find a prevalence of 0.8–10%.

3. What are the subtypes and syndromes of functional PNETs?

Insulinoma is the most common functional PNET and is malignant in <10% of cases. The most common presenting feature is hypoglycemia. The clinical presentation usually follows one of two patterns with either neuroglycopenic or adrenergic symptoms. These tumors occur in an even distribution throughout the pancreas.

Gastrinoma is the second most common functional PNET, causing the Zollinger-Ellison Syndrome (ZES). Approximately 60–90% are malignant. The most common presenting features are severe peptic ulcer disease, abdominal pain, and diarrhea. The vast majority (70–95%) of gastrinomas are located in the first portion of the duodenum and not in the pancreas as previous studies suggested.

Glucagonoma is the next most common type of functional PNET; 50–80% of these tumors are malignant. The most common presenting features are necrolytic migratory erythema (NME), diabetes, DVT, and diarrhea. These tumors occur in an even distribution throughout the entire pancreas and often present quite large and usually with metastases.

VIP-secreting tumors (VIPoma) are rare, malignant 40–70% of the time, and present with watery diarrhea, hypokalemia, and achlorhydria (WDHA, also known as Werner Morrison Syndrome). The most common tumor location is the body and tail of the pancreas.

Somatostatinomas are the rarest functional PNET and are malignant >70% of the time. The most common presenting symptoms are diabetes, steatorrhea, and cholelithiasis. These tumors are most commonly found in the pancreas (55%) or proximal small bowel (duodenum/jejunum, 44%).

4. What is Whipple's Triad?

Whipple's triad refers to the three presenting features of insulinomas including symptomatic hypoglycemia, serum glucose <50 mg/dl, and resolution of symptoms with restoration of glucose levels to normal by administration of glucose. This triad is not unique to insulinomas.

5. What are the principles of biochemical testing?

When a hormonally active PNET is suspected, this should be confirmed biochemically before imaging is performed. Imaging is not a diagnostic tool; imaging is only for PNET localization.

People suspected of having an insulinoma should have an outpatient 18-hour fasting protocol (if low pretest probability) or an inpatient 72-hour fasting protocol (if higher pretest probability) with measurement (during documented hypoglycemia) of plasma glucose, serum insulin, pro-insulin, C-peptide, β-hydroxy-butyrate, and an oral antidiabetic drug screen (sulfonylurea and meglitinides). This testing can be diagnostic but is informative only if hypoglycemia (glucose <55 mg/dl) if Whipple's triad has previously been firmly documented or glucose <45 mg/dl if Whipple's triad has not been previously documented.

People with suspected ZES should have fasting serum gastrin (FSG) levels measured. Proton pump inhibitors are known to increase serum gastrin and chromogranin A levels, potentially giving false positive test results. A normal FSG rules out gastrinoma. Patients with FSG >10 times the upper limit of normal should have gastric pH measured to differentiate gastrinoma from achlorhydria. Because many patients may not tolerate PPI withdrawal, an alternative evaluation may include FSG >10 times normal in combination with the identification of a NET by CT or endoscopic ultrasound (EUS), fine-needle aspiration (FNA) or fine-needle biopsy (FNB) with gastrin staining, or uptake on somatostatin receptor imaging.

Patients suspected of having a VIPoma or Glucagonoma should have a measurement of a serum VIP or glucagon level, respectively. If MEN is suspected, patients should also be evaluated for hyperparathyroidism and pituitary tumors as appropriate.

6. How should PNETs be imaged?

Multiphase CT scan or MRI with attention to the pancreas and liver is the first imaging modality. A noncontrast chest CT scan should also be done. Functional imaging using somatostatin receptor–positive emission tomography (SSTR-PET) with gallium-68 Dotatate can be done if there are suspicious findings. This can identify the primary tumor as well as metastatic spread. SSTR-PET can also be used to follow-up patients as an adjunct to conventional imaging. EUS and biopsy are not routinely necessary, but patients often present with this procedure having already been done. EUS ± FNA or FNB is only indicated if the diagnosis is in doubt, or the results will change management. EUS may be particularly useful for patients with negative CT or MRI. Because MEN patients have multifocal disease, EUS is useful for evaluating the extent of the tumor location in the pancreas.

7. Should functional lesions be resected?

Functional PNETs that are confirmed by biochemistry and are localized by imaging should be resected to control symptoms even when the tumors are small. Most PNETs, except insulinomas, also have high malignant potential.

8. Should nonfunctional PNETs be resected?

Asymptomatic patients with PNETs <1 cm can safely be observed. The very slow growth rate of PNETs allows for observation without missing the opportunity for a curative treatment window. PNETs >2 cm in size have a higher risk of liver metastases and therefore should undergo resection. Patients with tumors 1–2 cm in size need an individualized approach depending on age, comorbidity, details of imaging characteristics, change in size over time, the extent of resection needed, and shared decision-making.

9. What is the appropriate surgical approach for insulinomas?

Surgical excision of PNETs remains the only curative treatment. The often small size of insulinomas (<2 cm) along with the rarity of malignancy allows for a pancreatic parenchymal sparing excision by simple enucleation in most cases. It is becoming increasingly common to utilize a laparoscopic approach for simple enucleation. If a patient is not a candidate for enucleation (size, concerning features, proximity to the main pancreatic duct, contact with a major vessel), a pancreaticoduodenectomy for tumors in the pancreatic head or a distal pancreatectomy for tumors in the body or tail may be required. If the tumor cannot be localized with preoperative imaging, intraoperative ultrasound and bimanual palpation have up to a 95% sensitivity in localizing the tumor. Emerging approaches may involve EUS-directed radiofrequency ablation or ethanol injection.

10. Describe the surgical approach to gastrinomas.

The surgical approach to gastrinomas is more complex because these tumors are more frequently malignant, and the majority occur outside the pancreas. Tumors in the pancreatic head can often be enucleated, reserving formal pancreaticoduodenectomy for more invasive tumors or those in close proximity to the pancreatic duct or superior mesenteric vessels. Tumors in the body or tail of the pancreas are resected by distal pancreatectomy. Upper endoscopy with duodenal transillumination can aid with the identification of lateral wall tumors. A duodenotomy should be performed to reduce the risk of missing a gastrinoma located in the duodenal wall. Routine duodenotomy has also been shown to improve the long-term cure rate. Small submucosal lesions can be enucleated, but full-thickness resection of the duodenal wall may be necessary. These tumors have a propensity to metastasize to lymph nodes, and recent studies show that lymph node status not only has important prognostic value, but that resection of lymph nodes improves survival and reduces the risk of persistent disease. Thus, it is recommended that routine lymph node resection be performed in all gastrinoma cases.

11. Should PNETs occurring in patients with MEN1 be approached differently from PNETs occurring sporadically?

Yes. Approximately 70% of patients with MEN-1 develop PNETs, with gastrinoma being the most common. Gastrinomas are commonly multifocal in these patients and aggressive surgery can result in a biochemical cure. However, the morbidity and mortality rates of aggressive surgical resection combined with the availability of effective medical management of gastric hypersecretion sway many clinicians to avoid surgical resection unless there is suspicion of malignancy. It is recommended to avoid surgery for tumors ≤2 cm in size due to the low risk of hepatic metastases. For tumors >2 cm in size, the risk of hepatic metastases is much higher. The optimal surgical approach is controversial. The most common approach is duodenotomy for excision of duodenal wall tumors, enucleation of tumors in the head of the pancreas with systematic lymphadenectomy, and consideration of distal pancreatectomy depending on the presence or absence of multifocal tumors. Pancreaticoduodenectomy is recommended in select cases of large tumors in the pancreatic head that are not amenable to enucleation.

12. Describe the presentation of nonpancreatic GI neuroendocrine tumors (carcinoid tumors).

Carcinoid tumors can occur in many different organs throughout the body but most commonly occur in the GI tract (approximately 70% of the time). The tumor may present like all GI tumors with mechanical signs and symptoms (pain, obstruction) or from secreted hormones. In the GI tract, the most common locations listed in descending order are the small intestine, rectum, appendix, large intestine, and stomach. These tumors frequently result in a desmoplastic (fibrotic) reaction of the adjacent mesentery that causes bowel obstruction. Hindgut carcinoids do not usually produce active hormones and are typically found incidentally during endoscopy performed for other reasons. Gastric carcinoids are also frequently found incidentally on endoscopy but may also cause symptoms such as pain or bleeding. Neuroendocrine tumors of the small intestine are the most likely to result in carcinoid syndrome, which typically does not occur until the patient has developed metastases to the liver.

13. What is the classification of gastric carcinoids?

Gastric NETs are rare tumors even among other NETs. These tumors are associated with elevated gastrin and achlorhydria. There are four types:

I. The most common type (70–80%): often multifocal and associated with chronic atrophic gastritis. These are usually indolent in nature.
II. Multifocal and associated with ZES.
III. Aggressive type with a high rate of metastasis
IV. Single large, poorly differentiated malignancy

14. Describe the carcinoid syndrome.

Carcinoid syndrome results from the production and release of biologically active amines and peptides (such as serotonin, histamine, or tachykinins) from neuroendocrine tumors. Approximately 20% of tumors result in carcinoid syndrome. The liver metabolizes serotonin to inactive products, so most patients do not develop carcinoid syndrome until they have developed liver metastases, which permit serotonin to enter the systemic circulation. Carcinoid syndrome most commonly results from small bowel primary tumors. Classic symptoms include intermittent flushing, diarrhea, wheezing (from bronchoconstriction), and right-sided heart failure (from valvular fibrosis of the right-sided valves).

15. Once a patient is diagnosed with carcinoid syndrome, what is the next step?

Since serotonin is rapidly metabolized, it cannot be measured. However, 5-Hydroxyindoleacetic acid (5-HIAA) is the main serotonin metabolite and can be measured in 24-hour urine samples. Chromogranin A may also be a useful tumor marker.

Once diagnosed biochemically, the tumor must then be localized. This may be difficult because of the small size of most carcinoid tumors. Multiphasic CT or MRI and somatostatin receptor scintigraphy are generally recommended to localize carcinoid tumors. Luminal evaluation by endoscopy with consideration for EUS is also recommended for ileal, rectal, large intestine, and gastric carcinoids. An echocardiogram should be performed if right-sided heart disease is suspected in cases of carcinoid syndrome.

16. Describe the appropriate surgical management for nonpancreatic neuroendocrine tumors (carcinoid tumors).

Small intestinal carcinoids without metastases should be excised by segmental resection and lymph node dissection. Appendiceal carcinoids are typically incidentally discovered and occur most commonly at the appendiceal tip. Distal lesions smaller than 2 cm are adequately treated by appendectomy. The presence of a carcinoid near the appendiceal base, a size larger than 2 cm, or gross lymph node involvement requires formal right hemicolectomy. Rectal carcinoids often manifest with bleeding or are incidentally found on endoscopy. Tumors <1 cm can undergo endoscopic resection, tumors 1–2 cm can undergo transanal excision, and tumors >2 cm or with evidence of muscular invasion or lymph node metastases on EUS should undergo surgical resection (low anterior or abdominoperineal resection).

Types I and II gastric carcinoids account for most (>75%) gastric carcinoids and are associated with chronic hypergastrinemia resulting from chronic atrophic gastritis and Zollinger-Ellison syndrome, respectively. These tumors are most commonly small (<1 cm) and multifocal and are typically treated by endoscopic resection and surveillance with excellent outcomes. Octreotide or lantreotide in patients with ZES can control symptoms in Type II patients. Type III gastric carcinoids occur sporadically and are usually larger, solitary, and invasive. They are treated similarly to gastric adenocarcinoma with formal gastric resection and lymph node dissection. For tumors <2 cm in size endoscopic or wedge resection is possible. Type IV gastric carcinoids are managed by gastrectomy, when possible, followed by multimodal adjuvant therapy.

17. Discuss the role of surgery for liver metastases from neuroendocrine tumors (both pancreatic and nonpancreatic).

Cytoreduction using resection, radiofrequency ablation, or cryoablation is associated with improved symptom control and survival benefit. However, this is supported only by retrospective studies and is therefore controversial. Recent data suggest that >70% cytoreduction is equivalent to the previous standard of >90%. Treatment depends on patient age, comorbidity, number and location of lesions, rate of progression, and likelihood of symptom control. Simultaneous pancreas resection and liver cytoreduction can be done by experienced surgeons with acceptable morbidity and mortality in well-selected patients. However, if a pancreaticoduodenectomy is done first followed later by liver cytoreduction, the incidence of liver abscess with a previous biliary enteric anastomosis is much higher while the opposite is not observed. Therefore, if the procedures are to be staged it is better to do the liver-directed therapy followed by the biliary enteric anastomosis.

18. Is there a role for neoadjuvant therapy?

Neoadjuvant therapy should be considered in the following circumstances: vascular involvement, stage IV at diagnosis, borderline resectable well-differentiated tumor, and/or therapy optimization. However, there are no adequate prospective data. Capecitabine and Temozolomide or neoadjuvant peptide receptor radionuclide therapy (PRRT) should be considered depending on the situation (Chapter 61, 62).

19. What are the principles of systemic therapy in patients with unresectable or metastatic NETs?

Food and Drug Administration (FDA)-approved therapies for NETs include somatostatin analogs (SSA), everolimus, tyrosine kinase inhibitors, alkylating agents (capecitabine and temozolomide), and PRRT utilizing 177Lu-DOTATATE. SSAs (octreotide and lanreotide) bind to the somatostatin receptor (SSTR), promote cell cycle arrest and apoptosis, and inhibit tumor angiogenesis, growth factors, and hormone secretion. The long-acting release (LAR) forms are used for symptom management. There is no consensus on initiation of treatment in the asymptomatic patient with a low tumor burden. The use of octreotide or lanreotide in patients with clinically significant tumor burden or progressive disease can control tumor growth.

PRRT utilizes 177Lu-DOTATATE to target cells via the SSTR, resulting in improved progression-free survival. However, there are associated hematologic toxicities such as pancytopenia, myelodysplastic syndrome, and late hematologic malignancy.

Targeted therapy with everolimus (an inhibitor of mTOR) can be given with octreotide LAR. Tyrosine kinase inhibitors (sunitinib, pazopanib, lenvatinib, cabozantinib, axitinib, surufatinib) have shown only modest benefits. Cytotoxic chemotherapy with capecitabine and temozolomide improves progression-free survival in patients with metastatic disease. Lastly, belzutifan is an oral inhibitor of hypoxia-inducible factor (HIF) -2α which has been FDA-approved for VHL-associated cancers including PNETs.

KEY POINTS

Pancreas and Other GI Neuroendocrine Tumors

- The majority of PNETs are nonfunctional.
- Small (<2 cm) nonfunctioning PNETs can be safely observed.
- Insulinoma is the most common functional PNET, is usually benign, and in most cases can be treated by enucleation.
- Whipple's triad refers to the three presenting features of insulinoma including symptomatic hypoglycemia, serum glucose <50 mg/dl, and resolution of symptoms with restoration of a normal glucose level.
- Gastrinomas are usually malignant and can occur in the duodenum (most common), pancreas, and lymph nodes.
- Most commonly, carcinoid tumors develop in the small intestine, and metastases to the liver can result in carcinoid syndrome.
- Carcinoid syndrome is characterized by intermittent flushing, diarrhea, wheezing, and right-sided heart failure.
- PNETs in patients with multiple endocrine neoplasia type 1 (MEN1) are most commonly gastrinomas and are frequently multifocal. Tumors >2 cm should be resected.
- Cytoreduction of liver metastasis (>70%) from neuroendocrine tumors improves symptoms and prolongs survival.
- Systemic therapies for metastatic NETs include SSA, everolimus, tyrosine kinase inhibitors, alkylating agents, and PRRT.

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Bariatric Surgery

Kevin B. Rothchild and Jonathan A. Schoen

CHAPTER 68

1. Define obesity. How common is it?

Obesity is simply defined as the excess of body fat. The degree of body fat relative to weight is calculated by the body mass index (BMI – kg/m^2). Overweight is a BMI 25.0 to 29.9 kg/m^2; obesity is a BMI ≥30 kg/m^2; morbid obesity is a BMI ≥40 kg/m^2. Increasing BMI correlates with increasing health issues including diabetes mellitus, hypertension, sleep apnea and Pickwickian syndromes, asthma, coronary artery disease, cardiomyopathy, GERD, degenerative joint disease, hyperlipidemia, fatty liver (hepatic steatosis and NASH), gout, urinary incontinence, gallbladder disease, psychological disorders, menstrual irregularities, infertility, and certain cancers (endometrial, colon, breast, and kidney). Most importantly, a BMI >40 kg/m^2 increases the risk of death from all causes two fold. Approximately 64% or 127 million adults in the United States are considered overweight and 39.8% or 93 million adults are considered obese. Nearly 18.5% of children and adolescents are obese, with wide variation in certain regions.

2. In what populations is BMI limited as a precise indicator of obesity?

The utility of BMI alone is limited in those with a higher proportion of fat relative to muscle (i.e., the elderly) and in those with an unusually high proportion of muscle (i.e., bodybuilders).

3. How successful is nonsurgical treatment of obesity?

Evidence suggests that nonsurgical treatment (diet/behavior modification, exercise programs, and psychological support) for morbid obesity has a >90% long-term failure rate. Pharmacologic therapy for morbid obesity, although improving, has been hampered by serious side effects and lack of insurance coverage and, overall, has met with disappointing results.

4. What are the indications for obesity surgery?

In 2023, The American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) revised original 1991 consensus recommendations, stating the following patients be considered for bariatric surgery:

1. BMI ≥35 kg/m^2 for individuals regardless of presence, absence, or severity of comorbidities
2. BMI 30–34.9 kg/m^2 for people with metabolic disease or obesity-related comorbidities
3. BMI ≥27.5 kg/m^2 for the Asian population

5. Are there other important inclusion criteria for surgery?

The initial medical and surgical history and physical exam will determine a person's eligibility for bariatric surgery. The patient must meet the 2023 National Institutes of Health (NIH) Consensus Conference weight criteria. The patient must also clear psychological testing and evaluation and preferably have a referral from their primary care provider or internist. Endocrine disorders such as hypothyroidism and Cushing's disease should be ruled out, as should any medications causing weight gain. A documented history of failed prior weight loss attempts through dietary, behavioral, lifestyle, and/or medical interventions must be reviewed and verified. Last but most importantly, the patient must be motivated and have a basic understanding of the procedure, its risks, benefits, complications, and long-term outcomes prior to any further evaluation for surgery.

6. List the relative contraindications to bariatric operations.

1. Endocrine disorders that cause or contribute to morbid obesity
2. Psychological instability
3. Alcohol or drug abuse
4. End-stage organ disease unless used as a bridge to transplantation

5. Terminal cancer
6. Inability to comprehend or comply with postoperative nutritional and behavioral guidelines

7. Categorize the various surgical options for weight reduction.

I. Restrictive
II. Malabsorptive
III. Combination Restrictive/Malabsorptive
IV. Other

8. List the options for restrictive surgery.

1. Vertical-banded gastroplasty (historical): A stapling device divides the stomach vertically along the lesser curve to create a small (20 mL) pouch. A prosthetic device is then wrapped around the outlet of the pouch to prevent it from dilating over time. This operation is no longer performed due to poor long-term success, obstructive symptoms and reflux.
2. Gastric banding – Laparascopic adjustable (Figure 68.1): This procedure involves placement of an adjustable band around the proximal stomach to create a small (15 mL) pouch. The band is connected to a reservoir placed in the subcutaneous tissue that enables band adjustment. Concerns about long-term complications and variable weight loss success have led to a substantial decline in popularity, with many surgeons preferring the sleeve gastrectomy as a primary restrictive procedure.
3. Sleeve gastrectomy – Laparoscopic (Figure 68.2): This procedure is gaining in popularity and has now surpassed the gastric bypass as the most common operation done for weight loss. It involves stapling and removing a majority of the gastric body and fundus leaving the lesser curvature and a small amount of antrum. This amounts to approximately 80–85% of the stomach being excised and removed. The pylorus remains intact and the small intestine is unaltered. The short-term complications are essentially the same as for gastric bypass, but the long-term risks and side-effects are considerably less than for gastric bypass and biliopancreatic diversion. It is, however, less effective than these operations in regard to weight loss and resolution of diabetes and other comorbidities.

9. What are the options for malabsorptive surgery?

Biliopancreatic diversion with duodenal switch (BPD-DS) (Figure 68.3): A subtotal gastrectomy or sleeve gastrectomy is performed leaving a gastric remnant of 250–500 mL. The small bowel is divided 200–300 cm proximal to the ileocecal valve and the ileum is anastomosed to the stomach or first portion of the duodenum (duodenal switch). The jejunum is connected to the side of the

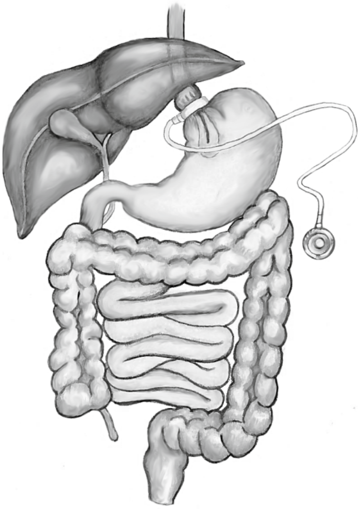

Fig. 68.1 Gastric Banding – Adjustable (Laparoscopic).

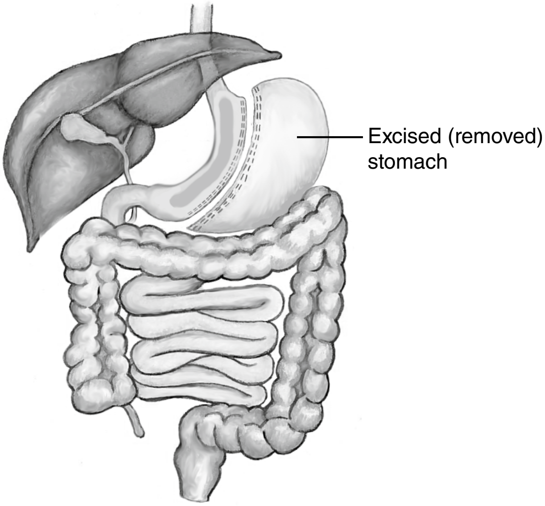

Fig. 68.2 Sleeve Gastrectomy (Laparoscopic).

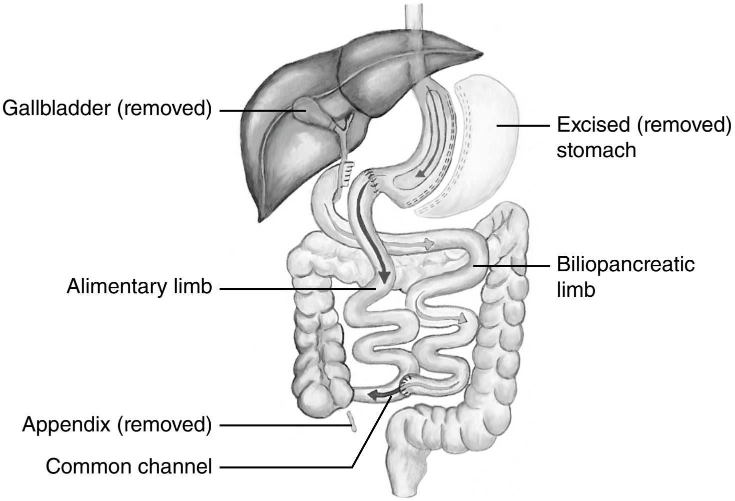

Fig. 68.3 Bilio-Pancreatic Diversion with Duodenal Switch (BPD-DS).

ileum approximately 50–100 cm from the ileocecal valve—the "common channel." This procedure results in malabsorption by creating a short common channel for digestion and absorption of food/calories. Chronic diarrhea is common if the patient is not very careful with diet. Similarly, a "distal" gastric bypass involves creating a short common channel leading to considerable malabsorption. These are the most effective options for weight loss and resolution of comorbidites but carry the highest short- and long-term risks. The biliopancreatic diversion has been gaining in popularity due to its excellent long-term weight loss results and is now being studied as a single anastomosis operation to decrease the morbidity and make it a more applicable option.

10. Explain the combined restrictive/malabsorptive option.

Roux-en-Y gastric bypass – Laparoscopic (Figure 68.4): The proximal stomach is stapled to create a small 15–30 mL proximal stomach pouch that is completely separated from the excluded remnant stomach. This small reservoir restricts the amount of food that can be ingested at one time, forcing portion control similar to the purely restrictive surgical options. The proximal jejunum is then divided distal to the ligament of Treitz and the distal end is anastomosed to the small stomach pouch (the Roux limb). The proximal end of the jejunum (the biliopancreatic limb) is then anastomosed to the side of the Roux limb (the "Y" connection) 75–150 cm distal to the gastrojejunostomy. The length of this Roux limb determines to a small degree the amount of calorie malabsorption; it is typically made longer for patients with high BMIs. There is malabsorption of vitamin and minerals from the bypass of the proximal jejunum. The effect of creating the Roux limb leads to dumping syndrome and forced aversion and avoidance of simple sugars and fatty foods. This operation causes weight loss due to portion control (restriction), dumping syndrome, and, to a lesser degree, malabsorption of calories.

The SADI (Single Anastamosis Duodeno-Ileal bypass) is a newer surgery that combines a sleeve gastrectomy with the duodenal switch for malabsorption, with the difference being that there is a longer common channel for nutrient absorption (250 cm) and a single-loop anastamosis at the post-pyloric duodenum, resulting in weight loss that is expected to be superior to the gastric bypass, without the significant incidence of malnutrition or vitamin deficiencies seen in the classic duodenal switch surgery (BPD-DS). Less marginal ulceration is seen compared to classic Roux-en-Y surgery as well.

11. What options are in the "other" category of procedures?

Vagal nerve stimulation, greater curvature plication, intragastric balloons, endoscopic gastric plication, gastrostomy tube placement, and gastric artery embolization have been studied as possible weight loss options but, as of yet, have not shown long-term results comparable to the surgical options already discussed and are generally not covered by insurance.

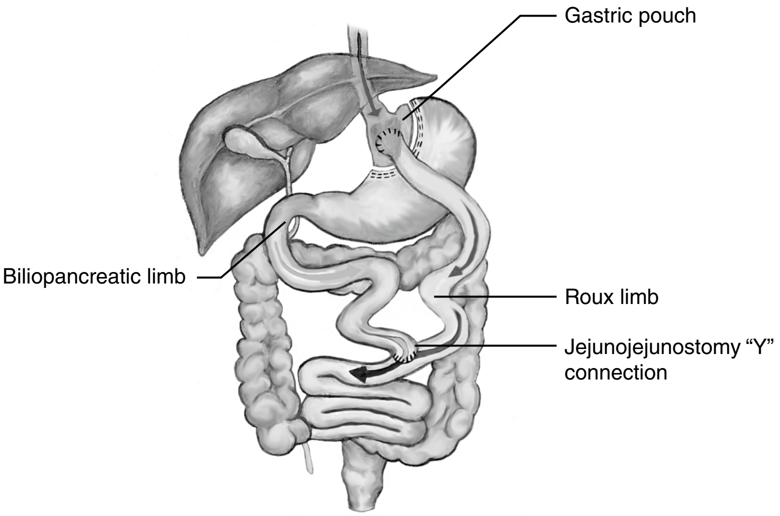

Fig. 68.4 Roux-en-Y Gastric Bypass (Laparoscopic).

Endoscopic procedures including gastric balloon and endoscopic sleeve gastroplasty (ESG), where endoscopic plication is used to mimic surgical sleeve gastrectomy, has shown efficacy with total body weight loss (TBWL) up to 15% in some trials at 12 months.

12. How much weight do patients lose following bariatric surgery?

Success following bariatric surgery is determined by both weight loss and improvement in obesity-related comorbidities. Most surgical studies report outcomes as percentage of excess weight lost (EWL) and consider loss of at least 50% of excess weight as a minimum criterion for success. The lap band typically produces 40–60% EWL gradually over 2–3 years but has up to a 50% failure and explant rate at 10 years. The gastric bypass typically produces 60–80% EWL rapidly over 2 years with fairly low rates of weight regain (approximately 10–15%) and an estimated 10% overall failure rate. The biliopancreatic diversion is the most effective weight loss procedure and results in the loss of 80% of excess weight maintained over the long term. Its popularity is limited by a small percentage of patients who have excessive weight loss or severe vitamin, mineral, and protein deficiencies. The sleeve gastrectomy has shown effective and durable weight loss, with up to 80% of patients achieving 60% EWL at 5 years. The SM-BOSS (Swiss Multicenter Bypass or Sleeve Study) was a prospective study that showed superiority of the gastric bypass over the sleeve with 65.9% EWL for the bypass at 10 years versus 56.1% for the sleeve. The biggest side effect of the sleeve operation was an increased incidence of de novo GERD.

13. What are the effects of bariatric surgery on obesity-related comorbidities?

Bariatric surgery has been shown to significantly reduce obesity-related comorbidities. Approximately 85% of patients with diabetes, hyperlipidemia, and obesity hypoventilation syndrome will have improvement or effective remission at 2 years postsurgery. Glycemic control occurs immediately and dramatically following bariatric surgery, especially after gastric bypass and biliopancreatic diversion, for reasons that are not entirely clear. This effect is largely due to dietary changes, adipose reduction with decreased cytokine production, and gastrointestinal hormonal changes. Hypertension, hyperlipidemia, sleep apnea, pseudotumor cerebri, and nonalcoholic fatty liver disease also improve or resolve in over two-thirds of patients after successful weight loss surgery. Salutary effects on other comorbidities, such as asthma, depression, arthritic pain, and even disability, are frequently observed following surgery.

14. Explain the incretin effect in relation to weight loss surgery.

Rapid transit of nutrients from the gastric pouch to the distal ileum in those with Roux-en Y anatomy or the duodenal switch causes increased release of incretins—Glucagon-Like Peptide-1

(GLP-1) and Glucose Dependent Insulinotropic Peptide GIP)—with subsequent enhancement of glucose-stimulated insulin secretion and ß-cell sensitivity to oral glucose, especially in patients with type 2 diabetes in whom this relationship is impaired. Similar effects are seen after the sleeve gastrectomy, although the results are less dramatic and substantial. This effect also suggests the possible role of Ghrelin as an incretin hormone, as this hormone level drops immediately after surgery. These early GI hormone changes likely explain much of the initial improvement in blood glucose levels following weight loss surgery. However, long-term data show that glycemic control can wane over time, likely due to weight regain or poor diet choices. This may also relate to the existing islet cell mass at the time of surgery, since the best and most durable responses occur in patients with diabetes for <5 years and not on insulin therapy. (see Chapter 12.)

15. Are GLP-1 Receptor Agonists (GLP-1 RA's) safe or useful after bariatric surgery?

Several studies have addressed GLP-1RA use in post–bariatric surgery patients with persistent diabetes (GRAVITAS), inadequate weight loss, or weight regain. Data supports use of these medications in this patient category, with results showing a significant increase in weight loss both early (within 6 months) and late (after 1 year), as well as a lowered HbA_{1c} in a wide range of bariatric procedures. Average weight loss exceeded 5% of baseline versus placebo, and side effects were minimal. (see Chapter 12.)

16. What are the complications of bariatric surgery?

Perioperative (30-day) mortality for bariatric procedures has fallen to approximately 0.1% overall, comparable to that for cholecystectomy or hip replacement. The laparoscopic technique has changed the pattern of perioperative complications. Wound complications and postop cardiopulmonary complications are less frequent, while anastomotic stenosis, gastrointestinal (GI) bleeding, and bowel obstruction occur more frequently with laparoscopic compared to open techniques. Mean hospital stay following laparoscopic bariatric surgery is 1–3 days, which is significantly shorter than after open surgery (5–7 days). Each procedure has its own unique risk of complications, with the Sleeve gastrectomy having the lowest number of serious complications (among stapled procedures), and the biliopancreatic diversion having the highest serious complication rate.

17. Give the incidence of complications following laparoscopic bariatric procedures in general.

- Anastomotic leak (1%)
- Anastomotic stenosis/stricture or marginal ulcer (RYGB) (5%)
- Postoperative bowel obstruction/Internal hernia (2%)
- GI bleed (1%)
- Gallstones (10%; SADI patients are recommended to have elective cholecystectomy approximately 6 months after initial procedure)
- Protein-calorie malnutrition (3–5%)
- Anemia (30%)
- Vitamin deficiency (30%)
- Wound complications (infection, dehiscence, and hernia) (4–5%)
- Band slippage or erosion into stomach (1–5%)

KEY POINTS

Bariatric Surgery

- Surgery is the only therapy that consistently results in significant, long-term weight loss in morbidly obese people.
- Laparoscopic sleeve gastrectomy is now the most common bariatric operation performed in the United States, followed by the laparoscopic Roux-en-Y gastric bypass. These procedures typically result in loss of 60–80% of excess weight (weight above ideal body weight).
- Surgical weight loss significantly reduces obesity-related comorbidities and is the most effective treatment for diabetes mellitus.

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Health Care Disparities in Endocrinology

Rocio I Pereira

CHAPTER 69

1. What are some common racial health and health care disparities in endocrinology among adults?

The most common and well-documented racial health disparities in endocrinology are in diabetes prevalence, management, and outcomes. Compared to non-Hispanic White adults, Black, Hispanic, and Native American adults in the United States are more likely to have type 2 diabetes (T2D), less likely to be prescribed standard-of-care medications or diabetes technology, less likely to meet recommended diabetes control targets, and more likely to experience diabetes complications. Mortality rates for Black adults with diabetes are twice as high as for non-Latino White adults with diabetes. Health and health care disparities have also been documented for obesity screening and treatment, osteoporosis outcomes, thyroid cancer outcomes, and mortality. More recent research has highlighted racial disparities in access to surgery for endocrine and pituitary disorders, health and health care disparities in the pediatric and sexual and gender minority populations, and race and gender disparities in exposure to endocrine disruptive chemicals.

2. How are the terms health equity and health disparities defined?

Health equity means that everyone, regardless of economic or social position, can be as healthy as possible. **Health disparities** are avoidable differences in health that adversely affect economically or socially disadvantaged groups. In the United States, health disparities have often referred to racial or ethnic health differences. However, health disparities also affect groups that are disadvantaged based on other social factors including economic situation, gender identity, sexual orientation, English language proficiency, physical or mental abilities, geographic location, etc.

3. Do racial health disparities reflect actual biological differences across racial/ethnic groups?

Over the past several decades, advances in medical, genetic, and behavioral sciences have uncovered the fallacy in a now outdated model of health disparities which incorrectly attributed disparities to genetic and behavioral factors (Fig. 69.1). Genetic and social science learnings have now made it clear that health disparities are instead caused by historical and persistent social inequalities. Race and ethnicity are social constructs, not biological ones, and racial and ethnic groups do not represent discrete genetic groups. In fact, there is more genetic variability within racial/ethnic groups than across them. Therefore, racial health disparities do not reflect actual biological differences across racial/ethnic groups. While genetic ancestry can still be informative when assessing genetic susceptibility, and ethnicity-targeted genetic screening continues to be useful in certain situations (e.g., carrier screening for individuals of Ashkenazi Jewish descent), race/ethnicity should be used cautiously, if at all, in determining individual screening, diagnosis, and treatment practices.

Similarly, racial/ethnic disparities are sometimes attributed to "cultural behaviors" that are associated with specific racial/ethnic groups, resulting in bias and unequal treatment. Biased assumptions about racial/ethnic differences in behaviors are particularly relevant to disparities in obesity and diabetes. While it is important for people to receive individualized counseling to eat a healthy diet and engage in physical activity, it is counterproductive for providers to assume that an individual is more likely to practice unhealthy behaviors simply because they are a member of a racial/ethnic group.

4. What are the major causes of health disparities in endocrinology and other clinical conditions?

Health disparities are linked to social factors, often referred to as **social determinants of health.** Social determinants of health can be divided into five categories: health care access and quality, neighborhood and built environment, social and community context, economic stability, and education access

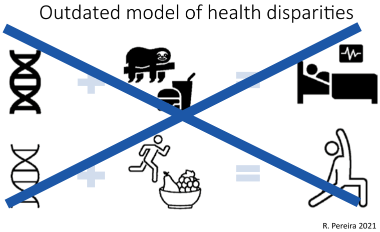

Outdated model of health disparities
R. Pereira 2021

Fig. 69.1 An outdated model for health disparities incorrectly attributed disparities to genetic and behavioral factors. Health disparities are instead caused by historical and persistent social inequalities.

and quality. Social barriers to health are more likely to impact individuals from minoritized groups in the United States due to past and current inequalities in social and educational opportunities and unequal treatment. For example, Black adults in the United States are less likely to own a home today due to unequal financial lending practices adopted by the Federal Housing Administration (FHA) and the Veterans Administration (VA) in the 1930s. The Residential Security Maps used by the FHA and VA to determine which mortgages to insure designated the majority of neighborhoods where Black Americans were living as "Hazardous" and color-coded these areas in red to distinguish them from neighborhoods that were "Best" in green, "Still Desirable" in blue, or "Declining" in yellow. This practice of "redlining" neighborhoods where Black Americans lived led to millions of Black Americans being denied home ownership. These disparities were subsequently passed on through intergenerational home ownership and wealth for non-Hispanic White Americans and growing poverty for Black Americans. The results of redlining are still apparent today, with only 42% of Black Americans owning homes compared to 73% of non-Hispanic White Americans, and family wealth for Black families, which is 15% of that of non-Hispanic White families. Geographic disparities in clinical outcomes in major US cities today continue to reflect the Residential Security Maps designations, with a higher prevalence of chronic diseases in previously "redlined" areas.

5. What is the difference between health disparities and health care disparities?

Health disparities are differences in health outcomes such as mortality, disease incidence and prevalence, and disease-specific outcomes. Health care disparities are differences in access to and quality of health care services such as health insurance coverage, screening and prevention services, medical provider visits, medications, etc. In 2002, the US Congress commissioned the Institute of Medicine (IOM) to investigate racial and ethnic health care disparities in the United States. The IOM committee found that "Racial and ethnic disparities in health care exist even when insurance status, income, age, and severity of conditions are comparable" and linked these health care disparities to significantly higher death rates from cancer, heart disease, and diabetes among racial and ethnic minorities compared to the non-Hispanic White population. Since 2003, the annual National Healthcare Quality and Disparities Report published by the Agency for Healthcare Research and Quality (AHRQ) has reported that Hispanic, Black, and American Indian/Alaskan Native individuals are more likely to experience lower-quality health care services for diabetes and other conditions. Health care disparities are among the social factors that lead to, and perpetuate, health disparities, along with other social determinants of health.

6. Describe disparities in diabetes affecting minoritized populations in the United States.

In the United States, the incidence and prevalence of T2D is higher in racial/ethnic minority/minoritized groups than in the non-Hispanic White population. Racial/ethnic disparities are also observed in the control of both type 1 diabetes (T1D) and T2D, as well as the incidence and progression of diabetes complications resulting in blindness, nontraumatic lower limb amputations, and kidney failure. Diabetes mortality in the United States is also much higher for American Indian/Alaskan Native, Black, and Hispanic populations compared to the non-Hispanic White population. A study of diabetes mortality rates in major cities in the United States found that diabetes mortality rates were, on average, twice as high for Black adults compared to White adults. The investigators estimated that inequities in diabetes mortality rates in the United States translated to more than 7000 excess Black adult deaths per year between 2013 and 2017.

7. How do social determinants of health impact diabetes care and diabetes outcomes?

Social determinants including poverty, low educational attainment, lack of health insurance coverage, living in neighborhoods with higher pollution, and having low social support have been linked to diabetes outcomes including higher diabetes incidence, worse diabetes control, higher incidence and progression of diabetes complications, and higher diabetes mortality. Social factors are correlated such that individuals facing one social barrier are often also impacted by one or more other social barriers, making it difficult to measure the individual effect of any single factor. In the Moving To Opportunity for Fair Housing Demonstration Project, women and children living in public housing in high-poverty areas were randomized to either receive housing vouchers they could only use to move to more affluent neighborhoods, vouchers they could use to move to any neighborhood, or no vouchers. After 10–16 years, the individuals who were given vouchers for more affluent neighborhoods were less likely to have an HbA1c in the diabetes range and less likely to have a BMI in the morbid obesity range. The correlated nature of race/ethnicity and the different social determinants of health have made it difficult to identify or measure the impact of individual social factors. While racial health disparities in diabetes are largely attributed to differences in social determinants aside from health care, unequal health care also contributes to these disparities.

8. How can providers support patients with diabetes who are facing social barriers?

Social determinants of health have an enormous impact on diabetes management, and consideration of social barriers is essential when formulating a treatment plan. Social barriers can prevent patients from following provider recommendations; this is often misinterpreted by the provider as the patient being “unengaged” or “noncompliant.” Patients who have unmet transportation needs, lack childcare options, or do not have money for copayments are more likely to miss or arrive late to their medical appointments, to not have labs drawn, or to not take their medications. These same factors can also be barriers to regular blood glucose monitoring if patients are unable to afford or pick up their testing supplies. Having food and/or housing insecurity can make it difficult to regulate carbohydrate intake or use insulin regularly. Asking patients about the barriers they may be facing allows providers to explore options and make shared decisions with the patient. Providers can support patients facing transportation barriers by not turning them away when they arrive late to a clinic appointment, arranging for telehealth visits, or linking them to a social worker to explore available transportation services. Medication access can be maximized by changing to generic medications, exploring formulary medication options, applying for medication prior authorization, ordering chronic prescriptions to be dispensed for 100 days at a time with refills for 1 year, or ordering prescriptions for shorter dispense periods if the patient is unhoused and unable to store large supplies of medication. Glucose monitoring can be encouraged by prescribing continuous glucose monitors or decreasing fingerstick check frequency to the minimal amount needed to inform care, giving clear instructions on the recommended timing of glucose checks. Finally, good nutrition can be encouraged by linking patients facing food insecurity to a social worker or to food pantry services, encouraging improvement rather than perfection, and recommending affordable healthy alternatives (frozen vegetables, avoidance of sugary drinks, less-processed foods).

9. How does patient mistrust of the healthcare system impact patient care and perpetuate health disparities?

Patient mistrust of health providers and the healthcare system can serve as an intrapersonal barrier to health care services and health. Non-Hispanic Black adults are less likely to trust their doctors and their health system than non-Hispanic White adults in the United States. Individuals with low trust in health care providers have fewer quality interactions with health care providers and have worse clinical outcomes. Provider behaviors that have been shown to build trust include communicating effectively (listening and providing detailed explanations), demonstrating empathy (treating patients as individuals, valuing their experiences, and showing commitment to solving their health issues), and demonstrating competence (being knowledgeable and thorough, and providing solutions for their health issues). When communicating with all patients, effective communication should include preparing with intention (reflecting on identity, bias, and power dynamics), listening intently and completely (including listening for the potential impact of social determinants of health on patient health), agreeing on what matters most (having explicit conversations about patient goals and prioritized outcomes), connecting with the patient’s story (acknowledging social and environmental factors influencing the patient's health, empathizing and acknowledging negative experiences), and exploring emotional cues (noticing and naming patient emotions, tuning into signs that a patient has experienced trauma).

10. How do health care disparities impact populations in the United States?

Unequal racial treatment has been documented in the management of both T1D and T2D in the United States. In a cohort study conducted at an academic center, adults with T1D who identified as Black were less likely to discuss, be prescribed, or use diabetes technology (such as continuous glucose monitors and insulin pumps), compared to adults with T1D who identified as non-Hispanic White. Similar racial disparities have been documented among youth with T1D and are linked to worse clinical measures for Black youth including higher HbA1c. Among adults with T2D who had clinical indications for use of SGLT2 inhibitors and/or GLP1 receptor agonists and for whom these medications were covered through their health insurance plan, those who identified as Black were less likely to be prescribed these medications compared to those who identified as non-Hispanic White. The use of continuous glucose monitoring technology is also lower among Black compared to non-Hispanic White individuals with T2D, even for those meeting current criteria for use. There are multiple drivers of provider medication-ordering behavior. Biased assumptions about whether a medication or technology is covered by an individual's health insurance likely contribute to inequitable provider behavior. In a study of a diverse safety-net patient population where individuals with T2D had access to continuous glucose monitors at no cost through their local Medicaid formulary, there were no racial disparities in provider prescriptive behavior or patient uptake. Furthermore, use of continuous glucose monitoring technology in this cohort was associated with improvement in HbA1c. These findings suggest that increasing access to continuous glucose monitoring technology may reduce disparities in diabetes control.

11. What endocrine health disparities and health care disparities have been documented for the pediatric population?

Non-Hispanic Black and Hispanic children are less likely than non-Hispanic White children to undergo evaluation for growth problems and they present with more severe conditions at the time of diagnosis. Girls are also less likely to see a subspecialist for evaluation for growth problems than boys and are more likely to require medical treatment when they are referred. Racial differences in pubertal development have been documented, with non-Hispanic Black girls entering puberty earlier than non-Hispanic White girls. Pubertal development in girls from other racial/ethnic groups and in boys has not been well studied. Non-Hispanic White children have a higher prevalence of T1D than children from racial/ethnic minority groups, but the percent change in incidence between 2002 and 2015 was higher for minority groups. Furthermore, racial/ethnic minority youth with T1D have higher rates of diabetic ketoacidosis (DKA) than non-Hispanic White youth. The incidence and prevalence of obesity and T2D are higher among children from racial/ethnic minority groups and are increasing at a faster rate than for non-Hispanic White children. Though race/ethnic minority youth are more likely to have obesity and T2D, they are less likely to undergo bariatric surgery.

12. What is known about racial and ethnic disparities in metabolic bone disease?

Racial and ethnic minority groups are less likely to be screened for osteoporosis and more likely to have higher disease morbidity. Black women are less likely to be screened for osteoporosis even after adjustment for socioeconomic status, insurance, comorbidities, and health care utilization. Though age-adjusted rates of diagnosed fracture are lower among Black women, severe complications of fracture, including prolonged hospitalization, loss of mobility, and death, are higher. Fracture risk calculators that adjust results based on race, and the use of White women as a reference when calculating T-scores, can potentially worsen disparities in osteoporosis diagnosis and treatment. Racial and ethnic health care disparities in screening and treatment of other metabolic bone diseases and skeletal complications of sickle cell disease are also pervasive in the United States.

13. Describe health and health care disparities affecting LGBTQIA (lesbian, gay, bisexual, transgender, queer, intersex, and asexual) youth and adults?

Some health disparities affecting sexual and/or gender minorities have been documented. However, this population remains largely understudied. In some parts of the United States, the health system continues to treat LGBTQIA people as if they are suffering from a mental health condition. Sexual orientation and gender identity information is still not collected routinely in health care or health research, making it impossible to fully characterize differences in care. Sexual minority individuals are at higher risk for overweight and obesity, disordered eating, anorexia, and underweight. Transgender youth have been found to have a higher risk of binge eating disorder and restrictive eating disorder.

14. How do disparities in access to high-volume surgeons and specialized care perpetuate endocrine health disparities?

Surgical management is clinically necessary for many endocrine conditions including thyroid cancer, severe Graves' hyperthyroidism, hyperparathyroidism, pituitary tumors, adrenal tumors, and neuroendocrine tumors. Clinical outcomes are most often determined by surgical quality, and the quality of endocrine surgeries is better in high-volume centers and when done by high-volume surgeons. However, a large majority of all patients have surgery by less experienced surgeons and in lower-volume centers. This is particularly true for Hispanic and Black patients, and the disparities in surgical quality are largest for the least common/more complicated procedures. For instance, 2% of Black and 1% of Hispanic patients have their thyroidectomies done by a high-volume surgeon compared to 7% of non-Hispanic White patients. For benign adrenal tumors, only up to 5% of Hispanic and 9% of Black patients had surgery by high-volume surgeons compared to up to 82% of White patients. Disparities are also observed for individuals in rural versus urban areas and for those in lower versus higher socioeconomic groups. These disparities in access likely contribute to higher complication rates, worse overall outcomes, and longer hospital lengths of stay for racial and ethnic minorities requiring endocrine surgery.

15. How did the COVID-19 pandemic highlight and exacerbate endocrine disparities in medical care?

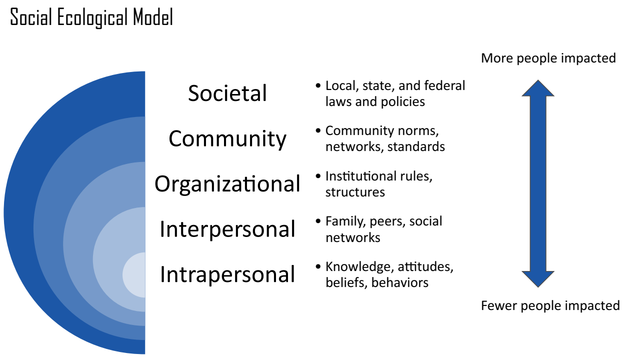
Diabetes and obesity are more prevalent among minoritized communities, and this contributed to higher mortality rates for these groups during the COVID-19 pandemic. These comorbidities, along with greater exposure to the virus associated with frontline jobs, reliance on public transportation, crowded living conditions, and lower access to testing and vaccination, resulted in much higher mortality rates and larger decreases in average lifespan for Black and Hispanic populations, particularly during the first year of the pandemic. Racial disparities in health care services also increased during the COVID-19 pandemic. As an example, Hispanic and Black non-Hispanic adults with diabetes had decreased rates of foot exams, flu vaccinations, and A1c checks compared to non-Hispanic White adults, and the disparities were greater in 2020 compared to 2019 (except for Black A1c, which improved in 2020 but was still lower than for the non-Hispanic White population).

16. What are endocrine–disrupting chemicals (EDCs) and how do they perpetuate endocrine health disparities?

EDCs are human-made chemicals that interfere with hormone action. Exposure to EDCs has been associated with endocrine disorders including obesity, diabetes, polycystic ovarian syndrome, thyroid dysfunction, adrenal dysfunction, nonalcoholic fatty liver disease, and reproductive dysfunction. Exposure to EDCs occurs through the food we eat (both in the food itself as well us through contamination during storage and reheating), the water or other liquids we drink, the air we breathe, the personal care products we use, and the materials our skin is in contact with. The more highly exposed groups for many/most EDCs include minoritized (Hispanic and Black) populations, women, and low-income families.

17. How can the use of race correction in clinical algorithms potentially perpetuate racial health disparities?

The false belief that race is a reliable proxy for genetic difference has been incorporated into many aspects of clinical practice, including the use of race-adjusted formulas to assess physiological function. One example relevant to endocrinology practice is the race adjustment in the equation to determine the estimated glomerular filtration rate (eGFR). The race adjustment results in higher eGFR values (suggesting better kidney function) for anyone identified as Black. This artificial adjustment can result in delayed diagnosis and treatment of kidney disease and disparities


Social Ecological Model
More people impacted
Societal
• Local, state, and federal laws and policies
Community
• Community norms, networks, standards
Organizational
• Institutional rules, structures
Interpersonal
• Family, peers, social networks
Intrapersonal
• Knowledge, attitudes, beliefs, behaviors
Fewer people impacted

Pereira 2021. Adapted from Frieden, T.R. (2010) *American Journal of Public Health, 100(4):590-595.*

Fig. 69.2 The Social Ecological Model argues that individual behavior is driven by factors at multiple levels: intrapersonal, interpersonal, institutional, community, and societal.

in kidney failure. Avoiding the use of race-adjusted eGFR would be expected to decrease the incidence of diabetic kidney disease and kidney failure among Black adults, which is currently three times higher than for non-Hispanic White adults.

18. How can the implementation of standard clinical processes and provider tools decrease health care disparities?

Evidence-based standards and guidelines for clinical management are available for most clinical conditions and are widely used by clinical providers. However, routine implementation of those standards for every patient often does not occur due to time constraints, focus on more acute clinical concerns, preconceived beliefs that the patient will not benefit or will decline, desire to avoid time-consuming prior authorization processes, lack of knowledge of standard practice, or other drivers of provider behavior. The establishment of standard workflows and the use of provider tools can assist clinicians in making standard-of-care services available to all patients. Standard workflows are particularly useful when they increase staff engagement in support of patients. For instance, implementing a workflow for the medical assistant to order a urine microalbumin test on behalf of the provider when due ensures routine screening for kidney disease in patients with diabetes. Provider tools embedded in the electronic health record can alert a provider when a patient is a good candidate for a certain class of medication. These processes and tools can help standardize practice behavior and ensure that all patients receive higher-quality care.

19. What is the social-ecological model framework and how does it inform the potential reach and impact of interventions to advance health equity?

The social-ecological model (Fig. 69.2) argues that individual behavior is driven by factors at multiple levels: intrapersonal, interpersonal, institutional, community, and policy. As providers, most of our influence occurs at an interpersonal level as we work with patients to prevent, diagnose, manage, and/or treat clinical conditions. At that level, advancing health equity implies ensuring that we provide the highest level of care to each of our patients. At an institutional level, we might implement a process to identify health disparities or to ensure standard workflows. At a community level, we can develop clinical guidelines that prioritize equitable treatment. Finally, at the policy level, we can advance equity by advocating for policies that expand access to medications or treatments.

20. How does the diversity of the clinical workforce impact health care disparities in endocrinology?

The US population is becoming more diverse. Between 2010 and 2020, the percentage of people who self-identify as non-Hispanic White decreased while all other groups grew as a percentage of the population. In 2020, 57.8% of people identified as non-Hispanic White, 18.7% as Hispanic, 12.1% as non-Hispanic Black, 5.9% as non-Hispanic Asian, 4.1% as non-Hispanic multiracial, and 1.4% as either non-Hispanic American Indian/Alaskan Native, non-Hispanic

Native Hawaiian/Pacific Islander, or some other race. Minority populations that grew in the last decade are also younger than the non-Hispanic White population. This increased diversity among children and working adults indicates a growing need for culturally and linguistically appropriate pediatric, obstetric, and mental health services. Higher rates of socioeconomic disadvantage among racial/ethnic minority groups also suggest a growing need to address social determinants of health in addition to health care needs. Racial concordance between patient and provider improves patient care, patient engagement, and patient satisfaction. Furthermore, providers from racial/ethnic minority groups underrepresented in medicine are more likely than nonminority providers to serve in minority and medically underserved communities. However, the racial/ethnic diversity of the healthcare workforce has not kept up with the change in the general population. Continued efforts to increase racial/ethnic representation in the health care workforce are needed.

KEY POINTS

- Health and health care disparities in the United States are driven by social and economic inequities and do not reflect biological or genetic differences.
- Inequities in social determinants of health, including health care access and quality, neighborhood and built environment, social and community context, economic stability, and education access and quality, perpetuate health and health care disparities.
- Health care providers can advance health equity by ensuring equitable access to high-quality services for patients from all socioeconomic groups and by considering social determinants of health and practicing shared decision-making in the development of treatment plans.

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CHAPTER 70

Endocrinology in Africa

Helen Yifter Bitew and Abdurezak A. Abdella

1. How prevalent is diabetes mellitus in Africa?

Low- and middle-income countries carry the major burden of diabetes worldwide. Eighty percent of people with diabetes live in these countries. In the International Diabetes Federation (IDF) Africa region, 24 million people are living with diabetes (prevalence of 5.3%), and this number is expected to increase to 55 million by 2045 (increment of 129%). However, considering that North Africa is not an IDF Africa region, the actual number of people with diabetes in the African continent is much higher than the number just reported. In addition, 54% of diabetes in Africa is undiagnosed, making this the highest percentage of undiagnosed people with diabetes in the world. There is a significant prevalence variation across different regions and countries within Africa, ranging from 1.1% in Benin to 12.3% in the United Republic of Tanzania. The five countries with the highest number of people with diabetes (age 20–79 years), according to the recent IDF report, are South Africa (4.2 million), Nigeria (3.6 million), Tanzania (2.9 million), Ethiopia (1.9 million), and Democratic Republic of the Congo (1.9 million). The five most populous sub-Saharan African countries (Nigeria, Ethiopia, DRC, Tanzania, South Africa) have varying diabetes prevalence rates of 3.6%, 5%, 5.8%, 12.3%, and 10.8%, respectively, among adults 20 to 79 years old. The five countries with the highest age-adjusted diabetes prevalence are Tanzania, Zambia, Comoros, South Africa, and Seychelles with 12.3%, 11.9%, 11.7%, 10.8%, and 8.5% prevalence, respectively. There were 53 million people with impaired glucose tolerance in 2021 with a projected rise to 117 million by 2045 (increment of 107%). Among risk factors, a high prevalence of HIV and combined antiretroviral therapy (cART) may contribute to the increased diabetes prevalence in sub-Saharan Africa as a result of ongoing inflammation and inherent mechanisms of cART despite achieving undetectable HIV viral levels. Moreover, because patients with diabetes are more prone to tuberculosis (TB), the next epidemic of TB cases in the region may be related to the increasing prevalence of diabetes. Further, during the COVID-19 pandemic, there was an observed increase in the number of insulin-requiring patients with diabetes, indicating the virus's potential role in driving diabetes occurrence. In the African region in 2021, 59,500 children and adolescents under the age of 20 years were living with type 1 diabetes; this is believed to be an underestimate.

2. What are the peculiarities seen among Africans with type 1 diabetes mellitus?

Although it is difficult to make generalizations about an entire continent and its people, a few peculiarities can be observed among Africans. Some studies have suggested that the frequency of antibody positivity among African patients with type 1 DM (T1DM) is lower than that reported in the American and European populations (7–44% versus 80–97%). One of the hypotheses for low antibody positivity with T1DM in Africa is the existence of malnutrition-related or modified DM as a cause of insulin-requiring DM. Some epidemiologic peculiarities include average age of onset that is later by about a decade, male predominance, and poor socioeconomic status correlated with higher risk.

3. What is malnutrition-related diabetes mellitus (MRDM)?

Although it is not in the current classification of diabetes, MRDM is noted in parts of sub-Saharan Africa and Asia. It was listed as a subtype of type 1 DM in the 1985 World Health Organization (WHO) classification but was later removed, with the citation that there was not enough evidence. There are two forms of MRDM: fibrocalcific pancreatic diabetes (FCPD) and protein-deficient pancreatic diabetes (PDPD; also known as the *Jamaica type* or *J-type*). It is reported that insulin requirements of patients with MRDM are higher than for typical patients with T1DM. African patients' insulin requirements tend to be less than those of Indian or Jamaican patients.

4. What are the features of MRDM in Africa?

The features suggestive of MRDM are onset before age 30 years, body mass index (BMI) <19 kg/m^2, absence of ketosis on insulin withdrawal, poor socioeconomic status, history of childhood malnutrition, and insulin requirements >2 U/kg/day (suggesting insulin resistance). FCPD will be diagnosed if, in addition to the above, the patient has a history of recurrent abdominal pain from an early age, pancreatic calculi on plain radiography of the abdomen, and/or typical changes on ultrasonography of the pancreas, in the absence of alcoholism, gallstones, or hyperparathyroidism.

5. Discuss ketosis-prone type 2 diabetes mellitus (T2DM).

A group of patients with the phenotypic T2DM appearance present with acute, severe hyperglycemia with ketosis. This phenomenon has been described among Africans and African Americans. It is characterized by a strong family history of T2DM, young adult age, male gender (three times more common in men than in women), rare islet autoimmunity, and high human papilloma virus-8 prevalence. Although insulin is required in the short term to control hyperglycemia, unlike classic T2DM, patients with ketosis-prone T2DM may achieve full remission with no need for continuing medical treatment. However, recurrence is possible.

6. How is a hyperglycemic crisis diagnosed and treated in resource-limited settings?

The diagnosis of diabetic ketoacidosis (DKA) is made on the basis of clinical presentation, blood glucose levels, and urine ketones. Serum ketones, arterial blood gas analysis, and serum electrolytes are not readily available. Most facilities administer regular insulin hourly because of lack of infusion capability and insulin analogues. This leads to increased complications. Missed doses of regular insulin result in patients taking days longer to clear their ketones. The long turnaround time to get results from laboratories adds further difficulty in following the DKA protocol. Finally, it is difficult to confirm resolution of DKA, often resulting in premature discontinuation of hourly insulin administration and subsequent DKA relapses.

7. How prevalent is gestational diabetes mellitus (GDM) in Africa?

There have been few studies in the sub-Saharan Africa (SSA) region on GDM. Earlier GDM prevalence reports from one systematic review range from 0% in Tanzania to 13.9% in urban Nigeria. A more recent report, from a systematic review and meta-analysis, showed a pooled prevalence of 14% in SSA with the highest prevalence of 20.4% in the central Africa region. There are variations of GDM prevalence within a region in SSA as seen in the East African countries of Rwanda 8.3%, Tanzania 5.9%, and Ethiopia 3.7%. This difference could be attributable to the use of different diagnostic criteria, screening strategy, and population characteristics. According to IDF, one in eight pregnancies in SSA are affected by hyperglycemia in pregnancy. Many SSA countries do not have screening and treatment protocols for GDM. However, there are increasing GDM care optimization initiatives across the continent with available resources. In addition to lifestyle modifications advised for pregnant mothers and dietary control, standard practice of treating with human insulin is mostly in use when needed and available. However, the oral agent Metformin is also used to treat GDM as an initial or add on to insulin without increasing reported fetal or maternal complications. Glibenclamide is considered in individual cases if sulfonylurea therapy is deemed beneficial. Safe oral anti-hyperglycemic agents may be preferred for the right patients because they are relatively inexpensive, less invasive, and require minimal self-monitoring of blood glucose (SMBG). SMBG is one of the biggest challenges in optimization of care for GDM in SSA in the public health facilities.

8. What is the most common cause of hospital admissions for patients with T2DM in Africa?

Diabetic foot disease (ulcers with/without gangrene) is the leading cause of hospital admission for people with T2DM in Africa. Neuropathy is not the most common cause of foot ulcers; instead, the cause for the majority of foot ulcers is unidentified. Poorly fitting shoes and blunt trauma contribute to one-third of cases. Foot ulcers result in significant morbidity/mortality, accounting for approximately 50% of amputations and >20% of in-hospital mortality. There is a rising combined burden of diabetes, infectious diseases, and chronic noncommunicable diseases affecting all social classes with different prevalences among the rich and poor and contributing to a major increase in morbidity and mortality.

9. How is diabetes care organized in Africa, and what are the care gaps?

The rate of undiagnosed DM in Africa is high. Patients usually present late, significantly increasing the chances of having chronic complications. In many African countries, care is integrated with other services at the primary care level. However, most centers fail to meet the IDF recommendations for resource-limited settings. The identified care gaps include limited number of health care professionals, patient overload, access to basic laboratories, self-monitoring of blood glucose, diabetes education, and access to and affordability of oral and injectable medications.

10. What options are there to manage diabetes in places where there are few endocrinologists/diabetologists?

A “task shifting/sharing” approach is increasingly being used in the management of chronic illnesses in areas with few specialized human resources for health care. A similar approach is used in the management of diabetes in Africa. Nurses, health care officers/medical officers, general practitioners, and internists are trained to provide comprehensive noncommunicable disease care. The fact that task sharing requires continuous support and mentorship from specialists has shaped the role of the endocrinologist in Africa.

11. What are the common thyroid disorders in Africa?

The leading cause of thyroid disorders in Africa is iodine deficiency. In addition to the low iodine status of the region, selenium deficiency and thiocyanate toxicity in inadequately cooked cassava contribute to iodine deficiency. Endemic goiter (>5% of 6- to 12-year-old children have goiters) is prevalent in different regions. The common causes for hyperthyroidism are toxic multinodular goiter, Graves’ disease, and toxic adenoma. The common causes for hypothyroidism are thyroidectomy, Hashimoto’s thyroiditis, and atrophic thyroiditis.

12. What is the impact of iodine deficiency in Africa?

The WHO recommends iodine intake of 150 mcg/day for the general population, 250 mcg/day during pregnancy, and 290 mcg/day when lactating. Two billion people, including 285 million school-age children, still have iodine deficiency (urinary iodine excretion of <100 mcg/L). This has substantial effects on growth and development and is the most common cause of preventable mental impairment worldwide. In areas where the daily iodine intake is below 50 mcg, goiter is usually endemic, and when the daily intake falls below 25 mcg, congenital hypothyroidism is common. Eight percent of newborns from sub-Saharan Africa are afflicted by learning disabilities resulting from iodine deficiency related disorders.

13. What are the challenges of diagnosing thyroid diseases in Africa?

Most diagnostic modalities are not readily available in sub-Saharan Africa. Thyroid function tests are in common use for assessment of functional status. However, radioactive iodine uptake measurements, thyroid scans, and thyroid antibody tests are rarely available. Ultrasonography is being used increasingly to characterize thyroid nodules. Fine-needle aspiration cytology (FNAC) is also available. Very few tertiary-level hospitals in SSA have nuclear medicine services for diagnostic and therapeutic purposes, with the latest being in Ethiopia.

14. What therapeutic options are available for treatment of hyperthyroidism and hypothyroidism in Africa?

Antithyroid drugs (ATDs) and surgery are the therapeutic mainstays for hyperthyroidism. Propylthiouracil is the main ATD in use, with limited availability of carbimazole and methimazole. There are centers that perform large volumes of thyroid surgery, the common indications being large goiters, retrosternal goiters, failure to respond to and control hyperthyroidism on ATDs, compressive symptoms, and thyroid malignancies. Radioactive iodine (RAI) therapy is not readily available. Very few tertiary high-end hospitals in SSA provide RAI therapy. Hypothyroidism is treated with levothyroxine (LT_4). The availability of liothyronine (LT_3) and different dose formulations of LT_4 is very limited.

15. How do you follow up a patient on an ATD in an African setting?

It takes more than a year for thyroid-stimulating hormone (TSH) levels to reach closer to normal values among African patients. This may be attributable to prolonged suppression of the thyrotropes from long-standing untreated hyperthyroidism, but other significant factors include repeated treatment interruptions caused by erratic availability of medications, the high cost of thyroid function tests forcing less frequent testing and adjustment of doses, and poor patient adherence. Therefore responses to treatment are followed mainly with free T_4 and $T_{3.}$

16. What are the comparative challenges in providing endocrinologic care other than that for diabetes in Africa?

Endocrinologic care in Africa is comparatively less developed and organized compared with diabetes care. There are challenges related to diagnosis, including laboratory assays for determining hormone levels, performing stimulation or suppression tests, and imaging (magnetic resonance imaging/computed tomography) of the endocrine glands. In addition, there are challenges for providing appropriate treatment because of lack of medications and less developed endocrine and neurosurgery services. There is lack of a sustainable supply of medications, such as bromocriptine; furthermore, cabergoline, hydrocortisone, fludrocortisone, growth hormone, and RAI treatment are not available at all in most sub-Saharan countries. These challenges have resulted in significant suffering of patients who have treatable endocrine diseases.

17. What training opportunities in endocrinology are available in Africa?

There are few specialist and subspecialty training programs in sub-Saharan Africa. Some parts of Africa have more developed endocrinology training programs (e.g., Egypt, Nigeria, and South Africa). However, in most SSA countries there are very limited training opportunities. Even when training opportunities are available, the capacity of programs to take large numbers of fellows is limited. In addition, the fact that the pool of medical graduates is small makes it difficult to attract many fellows into programs. In some African countries, such as Kenya, programs are focused only on pediatric endocrinology, whereas in others, such as Ethiopia, programs take candidates from adult and pediatric specialties. Recently, an adult endocrinology fellowship program was started in Rwanda.

18. What are the diagnostic challenges of thyroid cancer?

Most patients with thyroid nodules characteristically present late for care. The high prevalence of goiters has led to the general perception that thyroid nodules are benign conditions. In some places, goiters are even considered a mark of beauty. Even when patients present early, the absence of ultrasound-guided FNAC expertise and lack of availability of tumor genetic marker testing significantly affects diagnostic accuracy. The general lack of a multidisciplinary approach to care further complicates management after diagnosis.

19. How is thyroid cancer managed?

Once the diagnosis is made, care is generally directed to surgeons and then radiation oncologists. There is no access to RAI therapy or thyroglobulin tests for follow-up except in a few countries and mostly in a center where available. Most patients are followed-up by surgeons and radiation oncologists, effectively alienating endocrinologists from patients with thyroid cancer. This creates significant barriers to proper patient management and follow-up care with regard to LT_4 dosing required to achieve optimal TSH suppression and investigations needed to detect recurrence.

20. What are the peculiar roles and responsibilities of an endocrinologist in Africa?

Endocrinology is a comprehensive subspecialty; therefore, an endocrinologist in Africa cannot focus on specific endocrine pathology for subspecialization. In addition, she/he is expected to play more roles than purely that of an endocrinologist, including those of a general practitioner. Endocrinologists in Africa must be leaders, consultants, trainers, coordinators of care teams, and aggressive advocates for optimal health care for people in their communities and regions.

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CHAPTER 71

Pseudoendocrine Disorders: Recognition and Management

Michael T. McDermott

1. Define pseudoendocrine disorder.

"Pseudoendocrine disorder" does not have a distinct definition. Here the term is used mainly to describe proposed disorders that have never been scientifically proven to exist but that, due to widespread misinformation available on the Internet and other media, are relatively commonly diagnosed and treated with equally unproven and sometimes dangerous treatments. Alternatively, "pseudoendocrine disorder" can denote an endocrine diagnosis that was made erroneously as a result of conditions, medications, or supplements that adversely affect the accuracy of valid endocrine tests. A more complete discussion of all these issues can be found in our book, McDermott MT, ed., *Management of Patients with pseudoendocrine Disorders: A Case-Based Pocket Guide*. New York: Springer Nature, 2019.

2. What is adrenal fatigue?

Proposed by James L. Wilson in his 2001 book, *Adrenal Fatigue: The 21st Century Stress Syndrome*, adrenal fatigue is suggested to develop when the adrenal glands become unable to produce adequate amounts of adrenal hormones to deal with the daily stresses of life. It is said to occur in people who have chronic high stress (mental, emotional, or physical) in their work and/or family life. It is characterized by nonspecific symptoms such as fatigue, sleep disturbances, difficulty coping, body aches, digestive problems, and dependency on caffeine. Numerous practitioners and websites falsely promote this pseudoendocrine condition. Adrenal fatigue was featured on Dr. Oz on October 22, 2015.

3. How is adrenal fatigue diagnosed?

Affected people are encouraged to self-diagnose adrenal fatigue based on symptoms using scoring systems that are available on internet websites. Providers or patients themselves can also order a salivary cortisol profile in which multiple salivary cortisol samples are collected throughout the day and submitted to a lab for analysis (for a price); if the salivary cortisol levels fall below a normative line, the diagnosis of adrenal fatigue is said to be confirmed.

4. Is adrenal fatigue a real condition?

Adrenal fatigue has never been scientifically proven to exist. Symptom scoring systems or salivary cortisol profiles have never been tested scientifically or validated as tools to evaluate the function of the hypothalamic-pituitary-adrenal axis. As clinician-scientists, we must be open to novel ideas and proposals. However, rigorous verification by well-designed and well-conducted scientific investigations must still be the standard by which we evaluate and clinically apply new and innovative ideas. It is not sufficient, when patients' health and well-being are concerned, to simply propose a hypothesis and apply it without diligent scientific investigation.

5. How is adrenal fatigue treated?

Proposed treatments start with a healthy, well-balanced diet, regular exercise, good sleep habits, stress reduction, and cessation of smoking and alcohol use. Most of us would never object to any of these measures; this is the same advice we give to almost all patients. But adrenal fatigue websites and promoters also suggest that patients use reflexology, take licorice root, or use a variety of supplements that are claimed to improve adrenal function. However, there are also recommendations for and links to purchase "real" or "raw" adrenal extracts that contain bovine adrenal glandular extracts. The obvious potential for these products to cause secondary adrenal insufficiency is clearly a major concern.

6. What measures have been taken to educate the public about the adrenal fatigue myth?

The Endocrine Society (Hormone Foundation) has taken the lead in opposing the promotion of adrenal fatigue. The website and printed literature provide clear warnings, such as "No scientific proof exists to support adrenal fatigue as a true medical condition"; "Doctors are concerned that if you are told you have this condition, the real cause of your symptoms may not be found and treated correctly"; "Doctors urge you not to waste precious time accepting an unproven diagnosis such as 'adrenal fatigue' if you feel tired, weak, or depressed. If you have these symptoms, you may have adrenal insufficiency, depression, obstructive sleep apnea, or other health problems. Getting a real diagnosis is very important to help you feel better and overcome your health problem"; and "If you take adrenal hormone supplements when you don't need them, your adrenal glands may stop working and become unable to make the hormones you need when you are under physical stress. When these supplements are stopped, a person's adrenal glands can remain 'asleep' for months. People with this problem may be in danger of developing a life-threatening condition called adrenal crisis."

The Mayo Clinic website also has the following strong statements: "The term often shows up in popular health books and on alternative medicine websites, but it isn't an accepted medical diagnosis"; and "It's frustrating to have persistent symptoms your doctor can't readily explain. However, accepting a medically unrecognized diagnosis from an unqualified practitioner could be worse. Unproven remedies for so called adrenal fatigue may leave you feeling sicker, while the real cause—such as depression or fibromyalgia—continues to take its toll."

7. What is Wilson's syndrome?

Proposed by E. Denis Wilson in 1990, Wilson's syndrome is suggested to be present when people develop chronically impaired conversion of thyroxine (T4) to triiodothyronine (T3) as a prosurvival adaptation in response to stress. Susceptible people include famine survivors or their descendants (Scotch, Irish, Russian, Native American); holocaust survivors or their descendants; survivors of divorce, death of a loved one, or stress (family or job); chronic dieters; yeast sufferers; and people with hypoglycemia, eating disorders, and sleep disorders. The diagnosis is achieved by taking the axillary temperature with a mercury thermometer every 3 hours starting 3 hours after waking up; the body temperature readings are averaged over several normal days. If the mean body temperature is ≥1 degree below normal, the person "may" have Wilson's syndrome. The diagnosis does not involve testing TSH or thyroid hormone levels.

8. What is the proposed treatment for Wilson's syndrome?

The suggested treatment for Wilson's syndrome involves cycling the body temperature up to normal with "proper T3 thyroid supplements" (doses up to 100 mcg daily) and then cycling down again. The cycle is repeated until the body temperature remains normal after stopping T3 supplements; this typically takes 3–4 cycles but may involve 11–12 cycles in difficult cases.

9. What measures have been taken to educate the public about the Wilson's syndrome myth?

A 50-year-old woman died of an arrhythmia and heart attack while on amounts of thyroid hormone prescribed by Wilson; the Florida Board of Medicine accused him of "fleecing" patients with a "phony diagnosis." The Board and Wilson agreed to a 6-month suspension of his medical license, after which Wilson agreed to attend 100 hours of CME, submit to psychological testing, and pay a $10,000 fine.

The American Thyroid Association (ATA) states emphatically on its website that there is no scientific evidence to support the existence of Wilson's syndrome and that the proposed treatment is unsafe and frankly dangerous.

10. How is reverse T3 syndrome different from Wilson's syndrome?

Reverse T3 syndrome, which is similar to Wilson's syndrome, was proposed in a 2016 book and website, "Stop the Thyroid Madness." The proposal was not only that impaired T4 to T3 conversion reduces serum T3 levels but also that T4 is diverted into excess amounts of reverse T3 that then competes with T3 for the T3 receptor, further reducing peripheral tissue access to T3 action. Not only is there no scientific evidence to support the existence of this condition; there is well-documented and published evidence that T3 has 100-fold higher affinity for the thyroid hormone receptor than does reverse T3, and therefore even an excess of reverse T3 is not likely to be able to impair T3 binding. This book further proposes ways to "flush reverse T3 out of the body."

11. Explain the rationale behind low dose naltrexone therapy?

The notion that endogenous opioids and opioid antagonists may play a role in healing and tissue repair led to the use of low-dose naltrexone (LDN) as a possible treatment for numerous disorders. Dr. Bernard Bihari, "an LDN Pioneer and Champion," is featured in a 2002 online video describing his LDN work; an online tribute credits him with improving the lives and relieving symptoms in "tens of thousands (some say hundreds of thousands) of people with multiple sclerosis, rheumatoid arthritis, lupus, HIV/AIDS, autoimmune thyroid disease and even cancer." In her book, *Honest Medicine*, Julia Schopick proposes LDN as an "Effective, Time-Tested, Inexpensive Treatment for Life-Threatening Diseases" to include "multiple sclerosis, epilepsy, liver disease, lupus, rheumatoid arthritis, and other disorders."

12. What evidence supports the efficacy of low dose naltrexone?

A 2007 study published in the American Journal of Gastroenterology reported improvements in the Crohn's Disease Activity Index during 12 weeks of LDN treatment and for 4 weeks after stopping the medication in patients with active Crohn's disease. Other studies followed with mixed results. However, a 2018 Cochrane Database Systematic Review concluded there is "insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN for patients with active Crohn's disease." There is no valid evidence to support the use of LDN to treat autoimmune endocrine disorders.

13. Is it true that low testosterone in men can be a phony diagnosis?

Low testosterone or "low T" clinics have sprung up in many communities. Testosterone levels are not always done, since the diagnosis is often inferred by symptoms such as fatigue and low libido. Testosterone therapy is frequently recommended, sometimes in excessive amounts that result in frankly elevated serum testosterone levels that are known to be harmful. Failure to document true androgen deficiency before committing men to what may amount to lifetime testosterone replacement therapy is a serious disservice to these men. Furthermore, if hypogonadism is actually present, failure to investigate the cause is another serious disservice. Secondary hypogonadism is far more common than primary hypogonadism in men and is often due to other conditions such as opioid use, alcoholism, depression, sleep apnea, and various pituitary disorders that are far more dangerous than the low testosterone levels they cause. Failure to diagnose these conditions also deprives men of the opportunity to resolve hypogonadism by treating the underlying, and more serious, disorder.

14. What disorders can cause a pseudo-Cushing's syndrome picture?

Pseudo-Cushing's syndrome (PCS) results from nonneoplastic conditions that activate the hypothalamic-pituitary-adrenal axis and actually produce hypercortisolism and Cushingoid features. These conditions include alcoholism, depression, and poorly controlled diabetes. The usual screening tests for Cushing's syndrome (24-hour urine cortisol, 1-mg overnight dexamethasone suppression test, bedtime salivary cortisol) can all be positive in people with these conditions. However, adequate treatment of the disorders usually results in the resolution of hypercortisolism. Morbid obesity can also have many features suggestive of Cushing syndrome. But selective central obesity, proximal muscle weakness, bruising, and violaceous striae are usually not present with morbid obesity, and 24-hour urine cortisol excretion is usually normal.

15. How can estrogens cause false-positive testing for Cushing's syndrome?

Estrogen in oral contraceptive pills (OCPs) and pregnancy promote increased hepatic production of cortisol-binding globulin (CBG), which binds cortisol for transport in the circulation. Serum total cortisol levels are increased approximately 67% in women who take oral contraceptive pills;

pregnancy can cause similar elevations. This can cause false-positive testing for both baseline and dexamethasone suppressed serum cortisol levels. Tests that measure free cortisol (urinary free cortisol, salivary free cortisol) are not affected by OCPs or pregnancy.

16. What disorders can cause a pseudopheochromocytoma picture?

The term *pseudopheochromocytoma (pseudoPHEO)* has been applied to people who have symptoms resembling pheochromocytoma such as anxiety, tremors, palpitations, headaches, and sometimes hypertension but with completely normal levels of serum and urine catecholamines and metabolites. Treatment of these patients is reassurance. The term also applies to two situations in which catecholamines are actually elevated. Urinary metanephrine and normetanephrine levels in hospitalized patients (ICU and nonICU) can be very elevated with significant overlap with those in pheochromocytomas and paragangliomas. Therefore, elevated catecholamines and metabolites should be interpreted with caution in the setting of severe illness or hospitalization. Also, the use of levodopa/carbidopa for Parkinson's disease significantly elevates plasma and urine dopamine levels without affecting norepinephrine or epinephrine.

17. Is Hashimoto encephalopathy an accurate diagnosis?

Hashimoto encephalopathy (HE) is a misnomer referring to an acute encephalopathy of unknown cause that typically presents with symptoms of impaired mental status, somnolence, multiple stroke-like episodes, and seizures. It was previously termed "Hashimoto's encephalopathy" because many affected patients were found to have positive antithyroid antibodies in the serum and cerebrospinal fluid. However, the encephalopathy does not appear to be related to thyroid antibodies or thyroid dysfunction and responds well to steroid therapy. Therefore, that term is discouraged, and the condition has become more accurately referred to as *steroid-responsive encephalopathy associated with autoimmune thyroid disease (SREAAT)*.

18. Biotin interferes with some hormone assays. How significant is this in clinical practice?

Biotin is a reagent component for immunoassays of many hormones. People who take high doses of biotin supplements (5000–20,000 mcg/day for hair loss and brittle nails) can have falsely abnormal hormone measurements during biotin ingestion. High biotin concentrations can falsely elevate levels (free T4, free T3, TRAb, cortisol, testosterone, estradiol) in biotin-streptavidin competitive immunoassays and falsely lower levels (TSH, PTH, ACTH, LH, FSH) in biotin-streptavidin immunometric assays. Graves' disease can thus be erroneously diagnosed (low TSH, high free T4 and T3, positive TRAb) in someone taking high-dose biotin. An 8-hour abstinence from biotin often corrects this anomaly, but most authorities recommend ≥3 days of abstinence.

19. Describe a reasonable patient-centric approach to people who present with symptoms erroneously attributed to a pseudoendocrine diagnosis.

All providers will develop their own personalized approach that works best for their patients, but I find it best to always remember three crucial points: (1) The patient is not to blame for their diagnosis; like all others, they deserve our full attention and compassion. (2) The patient's quality of life is poor and he/she is frustrated. (3) It is an honor that she/he entrusts me with an opportunity to help them achieve better health and quality of life.

I listen attentively, perform a good physical examination, and offer additional testing if appropriate. I explore nonendocrine and psychiatric contributors to their symptoms. I understand and admit that current testing options do have some limitations. I recommend good nutrition, regular exercise, good sleep habits, and stress reduction for all patients. And I always provide honesty, encouragement, and compassion.

KEY POINTS

Pseudoendocrine Disorders

- "Pseudoendocrine disorder" refers to proposed conditions that have never been scientifically proven to exist but, due to widespread misinformation available on the Internet and other media, are relatively commonly diagnosed and treated with equally unproven and sometimes dangerous treatments.
- Adrenal fatigue is a nonexistent condition that supposedly results from adrenal exhaustion and atrophy due to chronic stress and has been promoted as a potential explanation for a variety of symptoms. Testing consists of nonvalidated online surveys and salivary cortisol profiles while treatment is not evidence-based at best and can be dangerous.
- Wilson's syndrome and reverse T3 syndrome are also nonexistent conditions that supposedly result from impaired T4 to T3 conversion and competition of excess reverse T3 with T3 for the T3 receptor. Testing involves the measurement of axillary temperature and treatment consists of T3 therapy, often at very high and dangerous doses.
- Low-dose naltrexone (LDN) therapy has been proposed as a treatment for multiple disorders involving autoimmune conditions and other disorders resulting from aberrant immune mechanisms, but there is no valid evidence that LDN has any benefits.
- Management of patients with pseudoendocrine disorders must involve careful listening, patient education, healthy lifestyle measures, and honesty, encouragement, and compassion.

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CHAPTER 72

Famous People With Endocrine Disorders

Pratima Kumar and Michael T. McDermott

1. **Name the former college basketball star from Gonzaga University who was diagnosed with type 1 diabetes mellitus (T1DM) at age 14 years.**
   Adam Morrison. After his final college season, Morrison shared college basketball's Player of the Year Award with J.J. Redick of Duke University. He was then selected third overall in the 2006 National Basketball Association (NBA) draft by the Charlotte Bobcats.

2. **This female track star recovered from Graves' disease and went on to win the title of "fastest woman in the world" at the 1992 Summer Olympics in Barcelona. Who is she?**
   Gail Devers. Devers repeated as champion in the women's 100 meters at the 1996 Olympics in Atlanta. She enjoyed remarkable longevity in her sport. In February 2007, at age 40 years, she won the 60-meter hurdles at the Melrose games with a time of 7.86 seconds.

3. **Name the dwarf actor who gained fame for his role as Tattoo on the television series Fantasy Island (1977–1984).**
   Herve Villechaize (1943–1993). Villechaize's short stature was secondary to achondroplasia. His adult height was only 3 feet, 2 inches.

4. **Television and film actress Mary Tyler Moore had what endocrine disorder?**
   T1DM. Moore was diagnosed at age 33 years. Her diabetes had been complicated by retinopathy and recurrent foot infections. She died as a result of pneumonia in 2017 at the age of 80 years. Diabetes was never an obstacle to her success as an actress.

5. **George H.W. Bush and his wife Barbara were both diagnosed with Graves' disease during his presidency (1989–1993). How did the president's Graves' disease manifest clinically?**
   Atrial fibrillation. Mrs. Bush's Graves' disease was also complicated by ophthalmopathy. In addition to radioactive iodine (RAI) for her hyperthyroidism, she also required treatment with glucocorticoids and orbital radiation therapy for her eye disease.

6. **Pulitzer Prize–winning film critic Roger Ebert was diagnosed with what endocrine disorder at age 59 years?**
   Papillary thyroid cancer (treated with thyroidectomy and RAI). Ebert had a major risk factor for papillary thyroid cancer. As a child, he was given radiation treatment for an ear infection. He was unable to speak, but he used a computer program to turn text into speech.

7. **Name the actor who had acromegalic gigantism and played the character Jaws in the James Bond films *The Spy Who Loved Me* (1977) and *Moonraker* (1979).**
   Richard Kiel (Kiel was 7 feet, 2 inches tall).

8. **Name the 2-foot, 8-inch dwarf actor best known for his role as Mini-Me in the film Austin Powers: *The Spy Who Shagged Me* (1999).**
   Vern Troyer. Troyer's dwarfism was secondary to chondrodysplasia. He had acting roles in >15 feature films.

9. **Name the NFL quarterback who developed T1DM in 2007.**
   Jay Cutler. He lost 35 pounds at the time of his diagnosis in 2007 but regained his weight and strength on insulin therapy. He performed athletically at the highest level despite having diabetes because of his devotion to good glucose control on and off the field.

10. Ancient Egyptian sculptures and paintings suggest that Tutankhamen (1357–1339 BC) and other pharaohs of the Eighteenth Egyptian Dynasty had what endocrine disorder?

Gynecomastia. Familial aromatase excess syndrome is a possible explanation for this historical finding.

11. What famous male ice skater overcame growth failure related to a childhood illness to win the gold medal at the 1984 Winter Olympics in Sarajevo?

Scott Hamilton. As a child, Hamilton suffered from Schwachman's syndrome, a rare disorder of the pancreas. His adult height is 5 feet, 3 inches. Hamilton was also diagnosed with testicular cancer at age 38 years and with a craniopharyngioma at age 46 years.

12. Name the late professional wrestler (and actor) who was well known for his height and acromegalic facial features.

Andre "The Giant" Rousimoff (1947–1993).

13. Charles Sherwood Stratton (1838–1883) reached an adult height of only 3 feet, 4 inches. What was his circus name?

General Tom Thumb. In 1863, Stratton married fellow diminutive circus performer Lavinia Warren, whose height was only 2 feet, 8 inches.

14. Actress Catherine Bell, who starred as Lt. Col. Sarah "Mac" MacKenzie on the television series *JAG* (1995–2005), has been treated for what thyroid disorder?

Papillary thyroid cancer.

15. Oscar award–winning actress Halle Berry was diagnosed with what endocrine disorder at age 21 years?

T1DM.

16. After successful treatment for Graves' disease, this professional golfer captained the United States team to the 1999 Ryder Cup in what has been called the greatest comeback in Ryder Cup history. Who is he?

Ben Crenshaw.

17. Vocalist Rod Stewart has had surgery for what endocrine disorder?

Thyroid cancer (most likely papillary). It took 9 months for Stewart to recover his voice after the surgery.

18. Ron Santo won six Golden Glove Awards and played in nine All-Star games while playing third base for the Chicago Cubs. He was diagnosed with T1DM at what age?

Eighteen years, just after signing his first contract to play major league baseball. Since his retirement from baseball, Santo has suffered the following macrovascular complications of his diabetes: coronary artery disease, requiring a quadruple coronary artery bypass operation and implantation of an automatic cardiac defibrillator device; and bilateral below-knee amputations for peripheral vascular disease. He died at the age 70 years in 2010.

19. Name the 3-foot, 7-inch, 65-pound midget who batted one time for the St. Louis Browns on August 19, 1951.

Eddie Gaedel (1925–1961). Gaedel was walked on four pitches by Detroit Tigers' pitcher Bob Cain.

20. Gheorghe Muresan of the Washington Bullets is the tallest player in the history of the NBA (7 feet, 7 inches). What treatments has he received for his acromegaly and gigantism?

Transsphenoidal pituitary surgery, pituitary radiation, and somatostatin analog injections. (Note: Shaquille O'Neal is 7 feet, 1 inch tall.)

21. Regardless of acting ability, it seems that every famous giant gets an acting role in a movie. Gheorghe Muresan starred in what movie with Billy Crystal?

My Giant (1998).

22. Which international soccer icon was diagnosed with growth hormone deficiency (GHD) as a child?

Lionel Messi was diagnosed with GHD at age 11. He took human growth hormone (HGH) injections during his childhood. At age 34, he led Argentina to win the 2022 FIFA World Cup.

23. The late actor Rondo "The Creeper" Hatton had severe acromegalic facial features. He played the villain in numerous horror films, such as The *Pearl of Death* (1944), *House of Horrors* (1946), and *The Brute Man* (1946). How old was Hatton at the time of his death?

Hatton died of a myocardial infarction at age 51 years. At the time of his death, he also reportedly suffered from diabetes and loss of vision. All these conditions were probably sequelae of his untreated acromegaly.

24. What endocrine disorder was Nick Jonas diagnosed with in 2005?

Pop singer Nick Jonas was diagnosed with T1DM in 2005 at the age of 13 years. He is currently involved in singing, acting, and songwriting.

25. Name the former chief justice of the US Supreme Court who died of anaplastic thyroid cancer at age 80 years.

William Rehnquist. Rehnquist was diagnosed with anaplastic cancer in October 2004, and he died <1 year later, in September 2005.

26. Grammy award–winning vocalists Johnny Cash (1932–2003), Ella Fitzgerald (1917–1996), Waylon Jennings (1937–2002), and Luther Vandross (1951–2005) all died of complications of what endocrine disorder?

Type 2 diabetes mellitus (T2DM).

27. Track star Carl Lewis competed in five consecutive Olympics. He is one of the five athletes who have won nine gold medals in an Olympic career. With what endocrine disorder was he diagnosed at age 35 years?

Primary hypothyroidism (secondary to Hashimoto's thyroiditis).

28. Name the American swimmer who was diagnosed with T1DM 18 months before he won two gold medals at the 2000 Olympics in Sydney, Australia.

Gary Hall, Jr.

29. Carla Overbeck, women's soccer star and captain of the 1996 US gold medal Olympic team, was diagnosed with what endocrine disorder at age 32 years?

Graves' disease.

30. Based on a true story, the film *Lorenzo's Oil* (1992) portrays a family's struggle with what rare adrenal disorder?

Adrenoleukodystrophy. The film's main character, Lorenzo Odone, was diagnosed with this condition at age 5 years.

31. Despite his T1DM, this former National Hockey League star led the Philadelphia Flyers to back-to-back Stanley Cup championships in 1973–1974 and 1974–1975.

Bobby Clarke. Clarke's diabetes was diagnosed at age 13 years.

32. The demanding Ironman Triathlon requires a 2.4-mile swim followed by a 112-mile bike ride and a 26.2-mile run. Name the three-time member of the US National Team for Long Course Triathlon who was diagnosed with T1DM at age 24 years

Jay Hewitt. Hewitt began competing in the triathlon after his diagnosis of diabetes.

33. Name the Supreme Court justice who has T1DM.

Justice Sonia Sotomayor was diagnosed with T1DM at age 7 years. She went to Princeton University and earned a law degree from Yale. She became the first Hispanic Supreme Court Justice in 2009 and is still serving her country in that capacity.

34. What Major League Baseball player broke the racial barrier in 1947 and became one of the greatest baseball players of all time despite having diabetes mellitus?

Jackie Robinson became the first African American athlete to play major league baseball when he joined the Brooklyn Dodgers in 1947. He led the league in stolen bases his first year and was the league's Most Valuable Player in 1949. Despite being diagnosed with T2DM while still in his baseball career, he became a Baseball Hall of Fame player and one of the greatest of all time.

35. What was the most likely reason for President Eisenhower's erratic blood pressure?

President Dwight D. Eisenhower, 34th President of the United States (1953–1961), suffered a heart attack while playing golf in Denver in 1955 and was hospitalized at Fitzsimons Army Medical Center. He died of ischemic cardiomyopathy 14 years later. His autopsy revealed a 1.5-cm pheochromocytoma in the left adrenal gland. The pheochromocytoma was the most likely cause of his erratic blood pressure.

36. What endocrine disorders plagued President John F. Kennedy?

President John F. Kennedy, 35th President of the United States (1961–1963), was diagnosed with Addison's Disease (primary adrenal insufficiency) in 1947 right after World War II, during which he was captain of the naval ship, PT 109. He was then diagnosed with primary hypothyroidism in 1955 and later with celiac disease and hypogonadism. He is thought to have had Autoimmune Polyglandular Syndrome type 2 (APS2). His medical records showed the following treatment regimen: hydrocortisone 10 mg AM, prednisone 2.5 mg BID, fludrocortisone 0.1 mg QAM, liothyronine 25 mcg BID, and methyltestosterone 10 mg PO QD.

KEY POINTS

- Because many endocrine disorders are common, it is not surprising that famous people have or have had endocrine disorders.
- Most endocrine disorders are either curable or treatable.
- Many famous people have accomplished great things despite their endocrine disorders. The lives of these famous people can serve as sources of encouragement to patients who suffer from similar endocrine conditions.
- Although T1DM is a serious disease, athletes with this condition have been able to compete and succeed at a professional level in almost every sport.
- The accomplishments of track star Gail Devers emphasize the excellent prognosis of properly treated Graves' disease.
- Perhaps the most fascinating of all endocrine disorders are the disorders of growth. This explains why dwarfs and giants have been so popular as circus performers and movie actors.
- The curability of most thyroid cancers is illustrated by the lives of Rod Stewart and Catherine Bell.
- The high mortality of untreated acromegaly is illustrated by the short lives of wrestler Andre "The Giant" Rousimoff and actor Rondo Hatton.

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CHAPTER 73

Interesting Endocrine Facts and Figures

Michael T. McDermott

1. Who is the tallest man on record?

The man with the greatest documented height was Robert Wadlow of Alton, Illinois. He was 8 feet, 11.1 inches (272 cm) tall and weighed 439 pounds (199 kg) when he died in 1940 at age 22; he was 7 feet, 8 inches (233.6 cm) at age 15. He had gigantism due to a growth hormone–secreting pituitary tumor that developed before epiphyseal plate closure. His feet were 1 foot, 6.5 inches (47 cm) long and he wore size 37 AA shoes.

2. Name the tallest woman on record.

Zeng Jinlian of Hunan Province, China, is the tallest woman on record. She was 8 feet, 1 inch (246 cm) tall just before her death at age 17 in 1982 and had been 7 feet, 1.5 inches tall at age 13. She also had a growth hormone–secreting tumor that developed during childhood. Her feet were 1 foot 2 inches (35.5 cm) long and her shoe size was 21.

3. How tall was the shortest man on record?

Chandra Bahadur Dangi of Nepal measured 21.49 inches (54.6 cm) tall in 2012. The shortest living man is Afshin Esmaeil Ghaderzadeh of Iran, who stood 2 feet 1.68 inches (65.24 cm) in 2022.

4. Who is the shortest woman on record?

The shortest adult woman on record was Pauline Musters of the Netherlands. She was 23.2 inches (approximately 61 cm) tall and weighed 9 pounds shortly before her death at age 19 years in 1895. Because of her relatively normal proportions, she is believed to have had pituitary growth hormone deficiency. The shortest currently living woman is Jyoti Amge of India, who stood 2 feet, 0.7 inches (62.8 cm) tall at age 18 in 2011.

5. Who had the most variable adult stature?

Adam Rainer of Austria was a 3-foot, 10.45-inch (118 cm) dwarf at age 21 years but rapidly grew into a 7-foot, 1.75-inch (218 cm) giant at age 32 years in 1931. He was 7 feet, 8 inches (234 cm) tall when he died in 1950 at age 51 years.

6. Which is the tallest tribe in Africa?

The Watusi (or Tutsi) tribe of Sudan, Rwanda, Burundi, and the Central African Republic are the tallest in the world. The men average 6 feet, 5 inches, and the women average 5 feet, 10 inches. Their tall stature is believed to be a genetic adaptation.

7. Which is the shortest tribe?

The Mbuti pygmies of central Africa have the lowest mean height. The men average 4 feet, 6 inches, and the women 4 feet, 5 inches. Their short stature is thought to result from genetic resistance to growth hormone, possibly due to deficient growth hormone receptors.

8. Who was the heaviest man on record?

Jon Brower Minnoch of Bainbridge Island, Washington, was 6 feet, 1 inch (185.4 cm), tall and weighed about 1400 pounds (635 kg) when he was admitted to a hospital at age 37 with heart failure. He remained in hospital for 2 years on a 1200-calorie diet and was discharged at 476 pounds (216 kg); his weight loss of 924 pounds (419 kg) is also a record. He weighed 798 pounds (362 kg) when he died in 1983 at age 42.

9. How much did the heaviest woman on record weigh?

The heaviest woman on record was Rosalie Bradford, who weighed 1199 pounds (543.9 kg) in 1987. She also holds the record for weight loss, having shed 917 pounds (416 kg) over the subsequent 7 years.

10. What is the greatest rate of weight gain ever recorded?

Arthur Knorr of the United States gained 294 pounds (134.7 kg) during the last 6 months of his life, an average weight gain of 1.6 pounds (0.73 kg) each day. Since a pound of fat has about 3500 kcal, this represents an excess intake (above caloric expenditures) of 5600 kcal a day. Doris James holds the record for women, having gained 328 pounds (148.8 kg) in the last year of her life (3150 kcal/day excess) before she died at age 38, weighing 675 pounds (306.2 kg).

11. What is the largest recorded waist size?

Walter Hudson of New York, who stood 5 feet, 10 inches (177.8 cm), had a peak weight of 1197 pounds (543 kg) and a waist size of 119 inches (302 cm).

12. Who are the heaviest twins on record?

Billy McCrary and Benny McCrary of Hendersonville, North Carolina, weighed 743 and 723 pounds (337 and 330 kg), respectively. Both had 84-inch (213 cm) waists. One brother died in a motorcycle accident, but the other is alive at the time of this printing.

13. What is the longest anyone has ever survived without food or water?

Andreas Mihavecz of Austria was put in jail in 1979. The guards forgot about him and gave him no food or water for 18 days, after which he was found still alive, albeit barely.

14. What is the greatest known number of children born to one woman in a lifetime?

Valentina Vassilyev, a peasant woman from Shuya, east of Moscow, Russia, gave birth to 69 children from 1725 to 1765. She had 27 pregnancies, producing 16 pairs of twins, 7 sets of triplets, and 4 sets of quadruplets. Sixty-seven of the children survived infancy. Her husband had 18 more children with a second wife.

15. Who is the oldest known woman to give birth?

Adriana Emilia Illiescu of Romania gave birth to a daughter by Cesarean section in 2005, at age 66 years, 230 days. Donna Maas of California is the oldest woman to give birth to twins, having delivered twin boys by Cesarean section in 2004 at age 57 years, 286 days.

16. What is the highest reported number of multiple births for a single gestation?

Ten births (decaplets) were reported in Brazil (1946), China (1936), and Spain (1924). Nine births (nonuplets) were recorded in Australia (1971), Philadelphia (1972), and Bangladesh (1977). The largest number to survive a multiple gestation is seven (septuplets), which has happened on three occasions; the mothers were Bobby McCaughey of Nebraska (1997), Nikem Chukwu of Texas (1998), and Hasna Mohammed Humair of Saudi Arabia (1998).

17. What is the highest single birth weight ever recorded?

Anna Bates, living in Seville, Ohio, gave birth to a 23-pound, 12-ounce (10.8 kg) baby boy who died 11 hours later in 1879. Anna was 7 feet, 5.5 inches (227 cm) tall. Carmelina Fedele of Italy gave birth in 1955 to the largest surviving baby, who weighed 22 pounds, 8 ounces (10.2 kg).

18. What is the oldest age to which a human has been documented to live?

Jeanne Louise Calment of Arles, France, lived to be 122 years and 164 days old. She died on August 4, 1997. The oldest man was Shigechiyo Izumi of Japan, who lived to be 120 years and 237 days old before he died in 1986.

19. What is the highest blood glucose level ever reported?

A 12-year-old boy with new-onset diabetes mellitus was still conscious when he was discovered to have a blood glucose level of 2350 mg/dL in 1995.

20. What is the record for most kidney stones produced by one individual?

Don Winfield of Canada passed 3711 kidney stones over a 15-year period (1986–2001).

21. What is the largest tumor ever reported?

A 328-lb ovarian cyst was removed from a woman in Texas in 1905.

22. What is the longest hair ever recorded?

Hoo Sateow of Thailand had his hair measured at 16 feet, 11 inches in 1997. He had not cut his hair for 70 years.

23. What is the record distance walked by an individual in 24 hours?

The record for men is 142.25 miles (229 km) by Jesse Castenda of the United States in 1976. The record for women is 131.27 miles (211 km) by Annie Van der Meer-Timmerman of the Netherlands in 1986. The 24-hour record for an individual in a wheelchair is 77.58 miles (125 km) by Nik Nikzaban of Canada in 2000.

24. Did King David of Israel have an endocrine disorder?

"When King David was old and advanced in years, though they spread covers over him, he could not keep warm. His servants therefore said to him, 'Let a young virgin be sought to attend you, lord king, and to nurse you. If she sleeps with Your Royal Majesty, you will be kept warm'. … The maiden, who was very beautiful, nursed the king and cared for him, but the king did not have relations with her" (I Kings 1:1–4). Some speculate King David was afflicted with hypothyroidism.

25. What endocrine disorder might Goliath of Gath have had?

Goliath of Gath, who was killed by a stone from David's sling (I Samuel 17:1–51), probably stood about 6 feet, 10 inches. His tall stature may have resulted from a growth hormone–secreting pituitary tumor. Others add that the ease with which David's stone became embedded in Goliath's skull may have been due to hyperparathyroidism, and his bizarre behavior may have resulted from hypoglycemia due to an insulinoma. He may thus be the earliest known case of multiple endocrine neoplasia type 1 syndrome.

26. What endocrine disorders did President John F. Kennedy have?

John Kennedy, 35th President of the United States (1961–1963), had Addison's Disease – primary adrenal insufficiency (1947), Hashimoto's Thyroiditis – hypothyroidism (1955), and Celiac disease. He likely had Autoimmune Polyglandular Syndrome Type 2 (APS-2). His medication regimen for these conditions was Hydrocortisone 10 mg QAM, Prednisone 2.5 mg BID, Fludrocortisone 0.1 mg QAM, Liothyronine 25 mcg BID, and Methyltestosterone 10 mg QD.

27. What US President had a pheochromocytoma?

Dwight D. Eisenhower, 34th President of the United States (1953–1961), had an acute myocardial infarction in 1955 while playing golf at Fitzsimmons Army Medical Center in Aurora, Colorado, the current site of the University of Colorado Denver School of Medicine and University of Colorado Hospital. Eisenhower died 14 years later of an ischemic cardiomyopathy. At autopsy, a 1.5-cm pheochromocytoma was discovered. It is not known if this tumor was ever symptomatic.

Website

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CHAPTER 74

Endocrine Case Studies

Michael T. McDermott

1. A 34-year-old woman has new-onset hypertension, BP 158/98. Serum potassium is 2.7 mEq/L. Hormone screening: plasma aldosterone (PA) 55 ng/dL (normal [nl], 1–16) and plasma renin activity (PRA) 0.1 ng/mL/hr (nl, 0.15–2.33). What is the probable diagnosis and what are the next steps?

Primary aldosteronism (Conn's syndrome) is strongly suggested by the presence of hypertension and spontaneous hypokalemia. Initial screening confirms this with a significantly elevated PA, a suppressed PRA, and a high PA/PRA ratio. Confirmatory testing with a saline infusion or oral salt loading test to assess the suppressibility of PA is often the recommended next step. However, the 2016 Endocrine Society Guideline Committee on Primary Aldosteronism recommended that confirmatory testing is not needed when all three of the following are present: spontaneous hypokalemia, suppressed PRA, and PA >20 ng/dl, because nothing else really causes this set of results. The next step is to establish whether the cause is an aldosterone-producing adenoma or bilateral adrenal hyperplasia; abdominal computed tomography (CT) should be ordered. Her abdominal CT scan showed a 2-cm left adrenal cortical adenoma with Hounsfield Units (HU) <10. Adrenal vein sampling (AVS) may be needed at this point if an accurate diagnosis is not apparent, but the 2016 guidelines also recommend that AVS is not needed if all three of the following are present: age <35 years, PA markedly elevated, unilateral cortical adenoma on an imaging study. She also meets these criteria. The treatment for an aldosterone-producing adrenal adenoma is surgery. Spironolactone and/or eplerenone should be given to control blood pressure and to normalize serum potassium preoperatively (Chapter 32).

2. A 32-year-old business executive develops amenorrhea. She has not recently lost weight but states that her job is very stressful. Lab Evaluation: serum estradiol = 14 pg/mL (nl, 23–145), luteinizing hormone (LH) = 1.2 mIU/mL (nl, 2–15), follicle-stimulating hormone (FSH) = 1.5 mIU/mL (nl, 2–20), prolactin = 6.2 ng/mL (nl, 2–25), thyroid-stimulating hormone (TSH) = 1.2 mU/L (nl, 0.5–5.0), and a serum pregnancy test is negative. A magnetic resonance imaging (MRI) scan of her pituitary gland is normal. What is the probable diagnosis and best management approach?

This patient has secondary amenorrhea with low estradiol and low gonadotropin levels. These results are most consistent with hypothalamic amenorrhea, which may occur in women who exercise excessively, have very low body weight, or have stressful jobs. The disorder results from reduced gonadotropin-releasing hormone (GnRH) pulse frequency in the hypothalamus. Treatment consists of stress management and, if menses do not resume, estrogen replacement therapy (Chapter 53).

3. A nulliparous 48-year-old woman presents with symptoms of thyrotoxicosis. She has a modest, nontender goiter and no exophthalmos. She takes no medications or supplements and has had no recent radiology procedures. Lab results: TSH <0.1 mU/L, free T_4 = 3.5 ng/dL (nl, 0.8–1.8), thyrotropin receptor antibodies (TRAB) negative, thyroglobulin = 35 ng/mL (nl, 2–20), ESR = 10 mm/hr and 24-hour radioactive iodine uptake (RAIU) = 1% (nl, 20–35%). What is the likely diagnosis and what are your management recommendations?

This 48-year-old woman has clinical and biochemical thyrotoxicosis with negative TRAB and a low RAIU. The differential diagnosis includes postpartum thyroiditis, silent thyroiditis, subacute thyroiditis, factitious thyrotoxicosis, and iodine-induced thyrotoxicosis. She has never been pregnant and denies medication use and recent iodine exposure. The nontender gland, elevated thyroglobulin, and normal sedimentation rate are most consistent with silent thyroiditis. A transient (1–3 months) thyrotoxic phase followed by a transient (2–6 months) hypothyroid phase is expected before the condition resolves; 15–20% of patients remain hypothyroid. If symptomatic, the thyrotoxic phase is best treated with beta-blockers, and the hypothyroid phase can be managed, if necessary, with temporary levothyroxine replacement (Chapters 39 and 41).

4. **A 38-year-old man has coronary artery disease, xanthomas of the Achilles tendons, and this serum lipid profile: cholesterol = 482 mg/dL, triglycerides (TG) = 125 mg/dL, high-density lipoprotein (HDL) cholesterol = 42 mg/dL, and low-density lipoprotein (LDL) cholesterol = 415 mg/dL. What is the probable diagnosis and what are the management options?**

   Significant elevations of total cholesterol and LDL cholesterol, normal TG, tendon xanthomas, and premature coronary artery disease are most consistent with a diagnosis of heterozygous familial hypercholesterolemia. Genetic mutations resulting in deficient or dysfunctional LDL receptors (LDLR) are the most common cause. Less common monogenic hypercholesterolemia disorders include apoprotein B mutations that produce a defective apo B that cannot bind to LDLR, proprotein convertase subtilisin-like kexin type 9 (PCSK9) mutations that cause accelerated LDLR degradation, LDLR adaptor protein 1 (LDLRAP1) mutations that prevent normal clustering of LDLR in cell surface clathrin-coated pits, and ATP-binding cassette G5 or G8 (ABCG5/8) mutations that cause abnormal cellular transport of cholesterol and plant sterols (sitosterolemia).

   The recommended criteria for diagnosing heterozygous familial hypercholesterolemia are the following: LDL >190 mg/dl (adults) or >160 mg/dl (children) *plus* premature coronary artery disease, or a first-degree relative similarly affected, or the genetic defect identified. Aggressive lipid lowering with a combination of statins and PCSK9 inhibitors is often required for satisfactory LDL control; ezetimibe and bile acid resins may be added if needed. In many cases, LDL apheresis is also indicated (Chapter 10).

5. **A 28-year-old man presents because of infertility. He has small, firm testes and gynecomastia. Laboratory results: testosterone = 171 ng/dL (nl, 300–1000), LH = 88 mIU/mL (nl, 2–12), FSH = 95 mIU/mL (nl, 2–12). What is the likely diagnosis and recommended treatment?**

   The man has hypergonadotropic hypogonadism. Small firm testes and gynecomastia are most consistent with a diagnosis of Klinefelter's syndrome. These men usually have a 47XXY karyotype, but mosaic patterns are also common. Androgen replacement therapy is the treatment of choice (Chapter 50).

6. **A 38-year-old nurse presents in a stuporous state; blood glucose is 14 mg/dL. Additional blood is drawn and she is quickly resuscitated with intravenous glucose. Further testing on the saved serum: insulin = 45 uU/mL, C-peptide = 4.2 ng/mL (nl, 0.5–2.0), proinsulin = 7 pmol/L (nl, <5). Sulfonylurea screen is negative. What is the probable diagnosis and what are the next steps in management?**

   This woman has hyperinsulinemic hypoglycemia. The differential diagnosis includes insulinoma, surreptitious insulin injection, and oral sulfonylurea ingestion. The elevated serum C-peptide and proinsulin levels are most consistent with an insulinoma. After an appropriate localizing procedure, surgical removal is the treatment of choice (Chapters 9 and 61).

7. **A 28-year-old woman presents for amenorrhea. Menses started at age 13 and became regular at age 16. She has type 1 diabetes mellitus. Further test results: estradiol = 15 pg/mL (nl, 23–145), LH = 78 mIU/mL (nl, 2–15), FSH = 92 mIU/mL (nl, 2–20), prolactin = 12 ng/mL (nl, 2–25), TSH = 1.1 mU/L; pregnancy test is negative. What is the most likely diagnosis and how would you treat her?**

   This woman has secondary amenorrhea with very low estradiol and elevated gonadotropin levels. In a patient with another autoimmune disease (type 1 diabetes mellitus), the most likely diagnosis is premature ovarian insufficiency (POI) due to autoimmune ovarian destruction. Hormone replacement therapy is the treatment of choice (Chapter 53).

8. **A 34-year-old woman presents with a milky breast discharge, amenorrhea, headaches, fatigue, and weight gain. Laboratory results: prolactin = 58 ng/mL (nl, 2–25), free T_4 = 0.2 ng/dL (nl, 0.8-1.8), TSH >60 mU/L (nl, 0.5–5.0). She has an**

enlarged pituitary gland on MRI. What is the cause of her elevated prolactin and what is the best treatment?

This woman has moderately increased serum prolactin levels, pituitary enlargement, and severe primary hypothyroidism. Her entire clinical picture is most likely explained by hypothyroidism, which is well known to cause secondary hypersecretion of prolactin and pituitary enlargement due to thyrotroph hyperplasia. All abnormalities should resolve after adequate thyroid hormone replacement is established (Chapters 25 and 40).

9. **A 6-year-old girl has developed breast enlargement and some pubic hair. She has not complained of headaches and has had good health otherwise. Her older sister entered puberty at approximately 8 years of age. Her height is at the 90th percentile for her age, and her physical examination reveals Tanner's stage III breast development and stage II pubic hair growth. Abdominal and pelvic examinations are normal. Laboratory results: LH = 7 mIU/mL (nl, 2–15), FSH = 8 mIU/mL (nl, 2–20), prolactin = 6 ng/mL (nl, 2–25), TSH = 1.9 mU/L (nl, 0.5–5.0), and a normal pituitary MRI. Bone age is 1.8 years ahead of chronologic age. What is the probable diagnosis and best management?**

   This girl has gonadotropin-dependent true precocious puberty. The etiology includes pituitary and hypothalamic tumors, but most cases in girls are idiopathic. The normal pituitary MRI points to a diagnosis of idiopathic precocious puberty. A long-acting GnRH analog should successfully arrest her premature development and allow her to enter puberty at a later, more appropriate time (Chapter 49).

10. **A 19-year-old man presents with excessive thirst and urination. Laboratory testing: glucose = 88 mg/dL, sodium = 146 mmol/L, osmolality = 298 mOsm/kg, and urine volume = 8800 mL/24 h. A water deprivation test is performed: urine osmolality = 90 mOsm/kg with no response to water deprivation and an increase in urine osmolality to 180 mOsm/kg after vasopressin administration. What is the likely diagnosis and what are your recommendations?**

    The differential diagnosis of polyuria and polydipsia with maximally dilute urine includes central diabetes insipidus, nephrogenic diabetes insipidus, and primary polydipsia. The lack of response to water deprivation and the more than 50% increase in urine osmolality after administration of vasopressin are most consistent with central diabetes insipidus. This may be caused by inflammatory or mass lesions in the hypothalamus but is often idiopathic. An MRI of the pituitary-hypothalamic region should be performed. The treatment of choice is intranasal or oral desmopressin (Chapters 22 and 29).

11. **A 45-year-old man has a 4-year history of worsening hypertension which has not yet been controlled with three antihypertensive medications. Serum potassium had been 3.7 mEq/L when his hypertension was first discovered. There is no family history of hypertension. Medications: Lisinopril 40 mg daily, Amlodipine 10 mg daily, HCTZ 25 mg daily. Vitals: BP 165/95 and P 72. Physical examination is otherwise normal. Recent labs: Na 144 mEq/L, K 2.5 mEq/L, Creatinine 1.1 mg/dL. Morning, seated Plasma Aldosterone (PA) was 24 ng/dL (normal: 1-21) and Plasma Renin Activity (PRA) was <0.6 ng/ml/hr (normal: 0.6–4.3). PA after a 2-liter saline infusion was 21 ng/dL. What do you recommend next for evaluation and subsequent treatment?**

    Primary aldosteronism (Conn's syndrome) is strongly suggested by the presence of resistant hypertension (uncontrolled on a 3-drug regimen that includes a thiazide diuretic) and easily provoked (thiazide diuretic) hypokalemia. Initial screening confirms this by finding a significantly elevated PA, a suppressed PRA, and a high PA/PRA ratio. Confirmatory testing with a saline infusion (or oral salt loading test) to assess the suppressibility of PA was indicated according to the 2016 Endocrine Society Guideline Committee on Primary Aldosteronism (confirmatory testing is not needed when all three of the following are present: spontaneous hypokalemia, suppressed PRA and PA >20 ng/dl); this patient had easily provoked but not spontaneous hypokalemia. The next step is to establish whether the cause is an aldosterone-producing adenoma or bilateral adrenal hyperplasia; abdominal CT showed bilateral but asymmetrical adrenal enlargement with the left side being significantly larger than the right.

The next step should be AVS since he does not meet the criteria for when AVS is not needed (all 3 of the following must be present: age <35 years, PA markedly elevated, unilateral cortical adenoma on imaging study). AVS did not show significant lateralization, indicating that the most likely underlying disorder is bilateral adrenal hyperplasia (idiopathic hyperaldosteronism). Management of this condition is an aldosterone receptor antagonist (spironolactone +/or eplerenone) and the use of other antihypertensive medications as needed to adequately control blood pressure. Aldosterone receptor antagonist therapy should be titrated until the serum potassium is normal without a need for potassium supplements and the plasma renin activity (PRA) is at the upper end of the reference range (Chapter 32).

12. A 25-year-old woman presents with a rounded face, prominent supraclavicular adiposity, and purplish striae in the axillae. Hormone testing: 24-hour urine cortisol = 318 ug (nl, 10–50); after 1 mg of Dexamethasone at bedtime, morning serum cortisol = 28 ug/dL (nl, 5–25); baseline morning plasma adrenocorticotropic hormone (ACTH) = 65 pg/mL (nl, 10–80). After an 8-mg oral bedtime dose of dexamethasone, the morning serum cortisol = 3 ug/dL. What is the probable diagnosis and what are the next steps for evaluation and management?

Cushingoid features and significantly elevated urinary cortisol excretion confirm the diagnosis of Cushing's syndrome. Endogenous Cushing's syndrome is most often caused by ACTH-secreting pituitary adenomas (65–80%), ectopic ACTH production by nonpituitary tumors (10–15%), and cortisol-producing adrenal adenomas (10–15%). The normal plasma ACTH level, which is inappropriate for the elevated serum cortisol level, and serum cortisol suppression with high-dose dexamethasone are most consistent with a pituitary adenoma (Cushing's disease). This should be confirmed with a pituitary MRI and, unless a pituitary adenoma ≥7 mm in size is identified; inferior petrosal sinus sampling should follow. Transsphenoidal surgical removal is the treatment of choice. When surgery does not result in remission, treatment options include repeat surgery, radiation therapy, and medical therapy with ketoconazole, metyrapone, or pasireotide to reduce cortisol production or mifepristone to block cortisol tissue action (Chapter 27). Metyrapone, pasireotide or osilodrosat to reduce.

13. An 8-year-old boy with known adrenal insufficiency complains of frequent muscle cramps and paresthesias of the lips, hands, and feet. Chvostek's and Trousseau's signs are positive. Lab results: calcium = 6.2 mg/dL (nl, 8.5–10.2), phosphorous = 5.8 mg/dL (nl, 2.5–4.5), parathyroid hormone (PTH) = 3 pg/mL (nl, 10–65) and 25-hydroxyvitamin D = 42 ng/mL (nl, 30–100). What is the most likely diagnosis and best treatment approach?

Hypocalcemia, hyperphosphatemia, and low serum PTH are diagnostic of primary hypoparathyroidism. This disorder, which is often autoimmune in nature, may occur in association with adrenal insufficiency as part of the autoimmune polyendocrine syndrome type I (APS I). Hypoparathyroidism must be treated with both calcium and calcitriol. Calcitriol is necessary because PTH, the missing hormone, is necessary for normal renal conversion of 25 hydroxyvitamin D into 1,25 dihydroxyvitamin D, the active vitamin D metabolite which is necessary for normal intestinal calcium and phosphorus absorption. A thiazide diuretic is also often helpful to further increase serum calcium and to reduce treatment-induced hypercalciuria (Chapters 20 and 59).

14. A 52-year-old man has a personal and family history of early coronary artery disease, minimal alcohol consumption, and no xanthomas on examination. Lab testing: cholesterol = 328 mg/dL, TG = 322 mg/dL, HDL = 35 mg/dL, LDL = 229 mg/dL, apoprotein B = 178 mg/dL (nl, 60–130), apoprotein E phenotype = E3/E3, TSH = 2.1 mU/L (nl, 0.1–4.5), and glucose = 85 mg/dL. What is the probable diagnosis and what are the treatment options?

This man has elevations of both serum cholesterol and TG and no detected disorders that cause secondary dyslipidemia. The differential diagnosis is familial combined hyperlipidemia and familial dysbetalipoproteinemia. The elevated apoprotein B level and the normal apoprotein E phenotype are most consistent with familial combined hyperlipidemia; an E2/E2 Apo B phenotype is characteristic of familial dysbetalipoproteinemia. The top treatment priority is LDL reduction. After LDL cholesterol is below the individualized goal, persistent TG elevations can be addressed with further dietary medication and weight loss and the possible addition of a fibrate, niacin, or fish oils (Chapter 10).

15. A 58-year-old man has recently developed diabetes mellitus, weight loss, and a skin rash that is most prominent on the buttocks; a dermatologist suspects this necrolytic migratory erythema and performs a biopsy that confirms this. What is the probable underlying diagnosis and what are the therapeutic options?

Diabetes mellitus, weight loss, and necrolytic migratory erythema are virtually diagnostic of a glucagon-secreting pancreatic neuroendocrine tumor (glucagonoma). The diagnosis can be confirmed by finding a significantly elevated serum glucagon level. After appropriate localizing procedures, treatment options include surgery for localized disease, somatostatin analogs (Octreotide LAR, Lanreotide) to reduce glucagon secretion, hepatic directed therapies (partial resection, hepatic artery embolization), chemotherapy (streptozotocin/doxorubicin), everolimus—an inhibitor of mTOR (mechanistic target of rapamycin), sunitinib and other VEGF-R inhibitors, and peptide receptor radionuclide therapy (PRRT) with ^{117}Lu. Chronic anticoagulation to reduce the increased risk of thromboembolic events and supplementation with zinc and amino acid infusions to reduce skin rash and improve quality of life should also be considered (Chapter 61).

16. A 29-year-old woman has asymptomatic hypercalcemia. Her mother and a sister also have hypercalcemia and have had failed neck explorations for presumed parathyroid tumors. Test results: serum calcium = 11.0 mg/dL (nl, 8.5–10.2), phosphorous = 3.0 mg/dL (nl, 2.4–4.5), creatinine = 0.9 mg/dL, intact PTH = 66 pg/mL (nl, 10–65), 25–hydroxyvitamin D = 42 ng/mL (nl, 30–100), 24-hour urine calcium = 13 mg (nl, 100–300), and creatinine = 1100 mg. What is the probable diagnosis and recommended management?

The vast majority of patients with hypercalcemia and a mildly elevated serum PTH level have primary hyperparathyroidism. However, in this case, the very low urinary calcium excretion and family history of unsuccessful parathyroid surgeries point to a suspected diagnosis of familial hypocalciuric hypercalcemia (FHH). The diagnosis is confirmed by finding a calcium/creatinine clearance ratio (urine calcium × serum creatinine/serum calcium × urine creatinine) of less than 0.01. This autosomal dominant disorder results from heterozygous inactivating mutations of the calcium sensor-receptor gene. The mutant sensor-receptors, present in parathyroid and renal tubular cells, have a raised threshold for calcium recognition. The result is a raised physiological equilibrium, in which hypercalcemia coexists with mild elevations of PTH and low urinary calcium excretion. The disorder causes no morbidity and does not require treatment (Chapters 17 and 18).

17. A 39-year-old HIV-positive man with Pneumocystis Jiroveci pneumonia (PJP) has the following serum thyroid hormone values: Free T_4 = 0.8 ng/dL (nl, 0.8–1.8), Total T_3 = 22 ng/dL (nl, 90–200), TSH = 0.5 mU/L (nl, 0.5–5.0) and T_3 resin uptake = 48% (nl, 35–45%). What is the most likely endocrine diagnosis and discuss its management?

The very low T_3, low-normal free T_4, low-normal TSH, and elevated T_3 resin uptake are most consistent with euthyroid sick syndrome (nonthyroidal illness syndrome). This is not a primary thyroid disorder but is instead a set of circulating thyroid hormone abnormalities that occur in the presence of nonthyroidal illnesses; it corrects when the underlying illness resolves. Treatment of the condition with thyroid hormone administration is not currently recommended, although this remains controversial (Chapter 45).

18. An 18-year-old female has not yet begun menstruating. She has a height of 56 inches, a small uterus, and no breast development. Laboratory results: estradiol = 8 pg/mL (nl, 23–145), LH = 105 mIU/mL (nl, 2–15), FSH = 120 mIU/mL (nl, 2–20), prolactin = 14 ng/mL (nl, 2–15), and TSH = 1.8 mU/L (nl, 0.5–5.0). What is the probable diagnosis and what are the management options?

Primary amenorrhea, short stature, low serum estradiol, and elevated gonadotropins are most consistent with a diagnosis of Turner syndrome. This disorder, characterized by ovarian dysgenesis, is associated with a 45XO karyotype. These women should be offered hormone replacement therapy with estrogen and progesterone. Growth hormone (GH) therapy should be considered because it improves longitudinal growth and final height (49 and 53).

19. A 62-year-old woman presents for recent nephrolithiasis and low back pain. Estimated calcium intake is 800 mg/day and she takes no vitamins. Physical examination is normal. Spine x-ray: compression fracture of the second lumbar vertebra (L2). Test results: serum calcium = 13.0 mg/dL (nl, 8.5–10.5), phosphorus = 2.3 mg/dL (nl, 2.5–4.5), albumin = 4.4 g/dL (nl, 3.2–5.5), PTH = 72 pg/mL (nl, 11–54), 24-hour urine calcium = 312 mg. What is the most likely diagnosis and best treatment?

Hypercalcemia, hypophosphatemia, and elevated or inappropriately normal serum PTH levels are diagnostic of primary hyperparathyroidism. Hyperparathyroidism is most often due to a solitary parathyroid adenoma, but familial syndromes (familial hyperparathyroidism, multiple endocrine neoplasia syndromes) usually cause four-gland hyperplasia. Surgical indications include serum calcium levels >1 mg/dL above the normal range, urinary calcium excretion >250 mg/24 hours in women and >300 mg/24 hours in men, renal impairment, osteoporosis, age <50 years, or symptoms related to hyperparathyroidism. Observation or bisphosphonate therapy may be appropriate for those with mild, asymptomatic disease or only mild bone loss. This woman should be referred for parathyroid surgery (Chapters 17 and 60).

20. A 32-year-old woman presents with a recent onset of fatigue, palpitations, sweating, and emotional lability. She gave birth 8 weeks ago. She is not breastfeeding her child. Pulse = 100/min. She has mild lid lag, a fine hand tremor, and a slightly enlarged, nontender thyroid gland. Laboratory results: TSH <0.03 mU/L (nl, 0.5–5.0), free T_4 = 3.8 ng/dL (nl, 0.8–1.8), and RAIU is <1% at 4 and 24 hours. What is the probable diagnosis and best treatment?

Thyrotoxicosis after pregnancy is most often Graves' disease or postpartum thyroiditis. TSH receptor antibody (TRAb) testing and the RAIU can distinguish the two. TRAb is positive and RAIU is high in Graves' disease while TRAb is negative (sometimes mildly positive) and RAIU is low in postpartum thyroiditis; an RAIU is contraindicated during breastfeeding. This woman has postpartum thyroiditis, a condition caused by lymphocytic inflammation with leakage of thyroid hormone from the inflamed gland. There is often a thyrotoxic phase (lasting 1–3 months) followed by a hypothyroid phase (lasting 2–6 months) and eventual return to euthyroidism, although 15–20% remain permanently hypothyroid. Treatment consists of beta-blockers, if necessary, for symptom control in the thyrotoxic phase, and levothyroxine for symptom control in the hypothyroid phase and for those who remain permanently hypothyroid (Chapters 39 and 41).

21. A 70-year-old man complains of weakness, weight loss, and hand tremors for the past year. He has been treated with amiodarone for 3 years for paroxysmal atrial flutter. Thyroid tests: TSH <0.01 mU/L (nl, 0.5–5.0), free T_4 = 3.35 ng/dL (nl, 0.8–1.8); RAIU 2.7% at 6 hours and 4.1% at 24 hours. A thyroid scan showed patchy tracer uptake. What is the likely diagnosis and best treatment?

This man has amiodarone-induced thyrotoxicosis (AIT). The condition occurs in up to 10% of people using amiodarone, which has a very high iodine content. There are two subtypes: type 1 AIT results from iodine overload and type 2 AIT results from amiodarone-induced thyroid follicular damage (thyroiditis). It can be difficult to distinguish the two types and there can be mixed cases with features of both types. AIT type 1 usually occurs in people with underlying goiters or nodules; RAIU is low but may be detectable and color Doppler studies show increased flow. AIT type 2 is more often seen in people without underlying goiters or nodules; RAIU is very low (often <1%) and color Doppler studies show decreased flow. Serum interleukin-6 is often elevated in type 2 AIT. Type 1 AIT is best treated with methimazole, though lithium and perchlorate (when available) may also add benefit, whereas type 2 AIT responds better to steroid therapy. Mixed or refractory cases may require methimazole and steroids, plasmapheresis, or thyroidectomy (Chapters 39 and 41).

22. A 20-year-old man presents for failure to enter puberty. He has small, soft testes, no gynecomastia, normal visual fields, and a decreased sense of smell. Laboratory results: testosterone = 40 ng/dL (nl, 300–1000), LH = 2.0 mIU/mL (nl, 2–12), FSH = 1.6 mIU/mL

(nl, 2–12), prolactin = 7 ng/mL (nl, 2–20), TSH = 0.9 mU/L (nl, 0.5–5.0). MRI of the pituitary gland is normal. What is the probable diagnosis and recommended treatment?

This picture is most consistent with idiopathic hypogonadotropic hypogonadism (IHH), also known as Kallmann syndrome when it is accompanied by anosmia. The disorder is due to a deficiency of GnRH and may be X-linked, autosomal dominant, autosomal recessive, or sporadic. The X-linked form results most commonly from mutations of the Kal-1 gene, which encodes anosmin, a neural cell adhesion protein that is critical for the scaffolding of GnRH neuron migration from the olfactory placode to the hypothalamus during embryonic development. This mutation also causes maldevelopment of the olfactory lobe resulting in anosmia. Mutations in Fibroblast Growth Factor (FGF) 8 or its receptor, FGFR1, or in the Kisspeptin/KissR system can underlie some cases of IHH. Androgen therapy is indicated to promote appropriate masculinization. When desired, these patients can also become fertile by receiving treatment with GnRH or gonadotropin preparations (Chapters 49 and 50).

23. **A 40-year-old man is brought to the ED with a sudden onset of inability to stand. He endorses recent muscle aches and weakness. Past medical history and family history are negative. He is a naturalized citizen originally from Korea. He takes no medications. Vitals: BP 124/68, P 88. Physical Exam: bilateral flaccid leg weakness (0/5), Bilateral proximal arm weakness (3/5), Reduced reflexes, Thyroid - diffuse goiter, Eyes - lid lag, no proptosis. Lab testing: TSH <0.01 mU/L (nl: 0.45–4.5), free T_4 2.52 ng/dL (nl: 0.8–1.8). What is His likely diagnosis and best management?**

This man was suspected to have thyrotoxic periodic paralysis (TPP). Serum potassium drawn during the episode was 2.1 mEq/L, confirming the diagnosis. TPP is a potentially fatal complication of hyperthyroidism that occurs as a sporadic disorder most often in Asian males. Episodes of mild to severe muscle weakness or paralysis associated with severe hypokalemia result from sudden intracellular shifts of potassium due to thyrotoxicosis-induced increased Na-K-ATPase pump sensitivity. TPP attacks are treated acutely with potassium supplementation (oral or IV) and beta blockers can be prevented by successful treatment of hyperthyroidism.

24. **A 32-year-old man complains of impotence and retro-orbital headaches for the past year. He is adopted and does not know his family history. He has bitemporal visual field loss. Physical exam is otherwise normal. Laboratory tests: serum calcium = 11.8 mg/dL (nl, 8.5–10.5), phosphorous = 2.5 mg/dL (nl, 2.5–4.5), albumin = 4.8 g/dL (nl, 3.2–5.5), PTH = 58 pg/mL (nl, 11–54), prolactin = 2650 ng/mL (nl, 0–20), testosterone 72 ng/dL, LH 2.1 mIU/mL (nl, 2–12), FSH = 1.1 mIU/mL (nl, 2–12). What is the likely diagnosis and how should this be further evaluated?**

This man has a prolactinoma, manifested by impotence, headaches, bitemporal hemianopsia, secondary hypogonadism, and a significantly elevated serum prolactin level. Hypercalcemia with an elevated serum PTH level indicates that he also has hyperparathyroidism. The MEN type 1 syndrome (MEN1), which consists of hyperparathyroidism, pituitary tumors, and pancreatic endocrine tumors, results from an inherited mutation in the Menin gene. This man should be screened for gastrinoma with fasting serum gastrin and for insulinoma by measuring serum glucose, insulin, c-peptide, proinsulin, and beta-hydroxybutyrate following an overnight fast or during a prolonged supervised fast. After pituitary imaging studies, he should be treated with a dopamine agonist, transsphenoidal surgery, or both, and subsequently with parathyroid surgery (Chapters 25 and 60).

25. **A 45-year-old man presented to primary care with progressive dyspnea on exertion. Hypercalcemia on lab testing prompted this referral. PMH: Hepatitis C. Medications: Interferon, ribavirin. Dietary Calcium: 600 mg/day. He takes no calcium or vitamin D supplements. Physical exam; diffuse pulmonary rales; normal otherwise. Lab testing: Calcium 12.4 mg/dL, Creatinine 1.2 mg/dL, CO_2 23 mEq/L, Phosphorus 5.9 mg/dL. Subsequent lab results: PTH <1 pg/mL, PTHrp <1 pmol/L, 25 OH Vitamin D 34 ng/mL (nl: 30-100), 1,25 (OH)2 Vitamin D 186 pg/mL (nl: 15-75). What is the likely cause of his hypercalcemia and what are the treatment options?**

This man's chest x-ray showed hilar adenopathy and diffuse interstitial disease; the biopsy revealed noncaseating granulomas consistent with sarcoidosis. He has calcitriol-mediated hypercalcemia.

Granulomatous disorders and lymphomas are the most common causes. In these cases, granulomatous tissue or lymphomas express high levels of 1 alpha-hydroxylase that converts circulating 25 (OH) Vitamin D into excess 1,25 (OH)2 Vitamin D, resulting in calcitriol-mediated hypercalcemia. Disorders responsible for calcitriol-mediated hypercalcemia are sarcoidosis (approximately 50% of cases), lymphoma (approximately 17%), granulomatous infections (approximately 8%), other granulomatous diseases (approximately 4%), idiopathic (approximately 3%) and CYP24 mutations (<1%). Treatment consists of hydration and glucocorticoids; ketoconazole or hydroxychloroquine can be added if these measures are not sufficiently effective (Chapters 17 and 19).

CYP24 Mutations named correctly?

26. A 52-year-old woman complains of progressive fatigue, puffy eyes, dry skin, and weight gain over the past year. Acromegaly was treated with transsphenoidal surgery and radiation therapy 10 years ago. Physical exam: normal visual fields, mild periorbital edema, and dry skin. Laboratory testing: GH = 1.2 ng/mL (nl, <2.0), insulin-like growth factor 1 (IGF-1) = 258 ng/mL (nl, 182–780), TSH = 0.2 mU/L (nl, 0.5–5.0), free T_4 = 0.3 ng/dL (nl, 0.8–1.8). What is the likely cause of her symptoms and what is the best treatment?

She has central hypothyroidism due to pituitary damage from the combined effects of surgery and radiation therapy of her acromegaly 10 years earlier. Such a lengthy delay in the development of this condition is not uncommon. The most common causes of central hypothyroidism are tumors, surgery, radiation, hemorrhage, infections, infiltrative disorders, and traumatic brain injuries affecting the hypothalamus or pituitary gland. Medications can also suppress TRH or TSH production and cause central hypothyroidism: opioids, glucocorticoids, mitotane, and bexarotene. Metformin has also been reported to suppress TSH secretion modestly, but so far has not been reported to cause de novo central hypothyroidism.

Central hypothyroidism is diagnosed based on symptoms of hypothyroidism, low serum T4, and low or low-normal serum TSH. Treatment is levothyroxine replacement in doses sufficient to relieve symptoms and maintain serum-free T4 levels in the upper half of the normal range. Because TSH secretion is impaired, serum TSH levels cannot be used to monitor the response to therapy. Assessment of her pituitary-adrenal axis is also indicated (Chapters 22 and 40).

27. A 32-year-old woman complains of bilateral deep thigh pain. She has had type 1 diabetes since age 20. She has two to three bowel movements each day. Menses are regular. Her diet is well balanced with adequate calcium intake and she takes a multivitamin. Physical examination is normal. Laboratory results: serum calcium = 8.2 mg/dL (nl, 8.5–10.5), phosphorous = 2.3 mg/dL (nl, 2.5–4.5), alkaline phosphatase = 312 U/L (nl, 25–125), PTH = 155 pg/mL (nl, 11–54), 25 hydroxyvitamin D = 7 ng/mL (nl, 30–100). Explain these findings and suggest a probable diagnosis and treatment plan.

Her biochemical profile of hypocalcemia, hypophosphatemia, elevated alkaline phosphatase, and significant secondary hyperparathyroidism suggests vitamin D deficiency, which is confirmed by the low serum 25-hydroxyvitamin D level. The elevated serum alkaline phosphatase suggests that the vitamin D deficiency has been sufficiently severe and prolonged to result in osteomalacia. Lactose intolerance can cause chronic diarrhea but seldom results in vitamin D and calcium malabsorption. Celiac disease (gluten-sensitive enteropathy), which occurs with increased frequency in people with type 1 diabetes, should be suspected. The diagnosis can be confirmed by measurement of tissue transglutaminase antibodies or a small bowel biopsy. Treatment is the elimination of dietary gluten (wheat, rye, barley, and oats) and supplementation with calcium and vitamin D.

28. A 31-year-old woman is referred for abnormal thyroid tests ordered to evaluate fatigue, insomnia, and headaches for 6 months. Vitals: BP 132/73, P 72, Ht 5’8”, Wt 139 lb. Physical exam: diffuse goiter and warm moist skin; eyes normal. Lab tests: TSH 4.74 and 5.04 mU/L (nl: 0.45–4.5), Free T_4 2.91 and 2.82 ng/dL (nl: 0.8-1.8). What is the differential diagnosis and what do you recommend next?

Elevated or normal serum TSH levels in the presence of elevated serum T_4 levels are clearly inappropriate. The following causes of inappropriate TSH levels should be considered: thyroid hormone resistance syndromes, TSH-producing pituitary tumors, human antimouse antibodies (HAMA), Macro-TSH, and high-dose biotin supplements.

She confirmed that she was not taking biotin supplements. TRAb was negative. HAMA testing was negative. An alpha subunit (ASU) was elevated at 1.4 ng/ml and the ASU/TSH molar ratio was >1.0. MRI showed a 2.4 cm pituitary tumor that abutted the optic chiasm. Pituitary surgery was performed and the tumor stained heavily for TSH and ASU. Final diagnosis: TSH-producing pituitary adenoma (Chapters 28 and 39).

29. A 42-year-old man presents for evaluation of a new skin rash. He has type 2 diabetes. He drinks two to three beers most nights. Physical examination shows red papules with golden crowns most prominently on the buttocks, thighs, and forearms. Laboratory results: glucose = 310 mg/dL, hemoglobin A_{1c} (HbA1C) = 12.9%, cholesterol = 1082 mg/dL, and TG = 8900 mg/dL. Discuss the cause, risks, and treatment of this lipid disorder.

This man has eruptive xanthomas and severely elevated serum triglycerides (TG). This usually results from the combination of an inherited TG disorder (familial hypertriglyceridemia or familial combined hyperlipidemia) with a secondary cause of TG elevation (uncontrolled diabetes, excess alcohol use). LDL cholesterol cannot be accurately assessed with TG levels this high. Since he is at high risk of developing acute pancreatitis, the priority is to quickly lower the serum TG level to <1000 mg/dL. This can be achieved most effectively with a temporary very low fat (<5% fat) diet, glucose control (may require a temporary insulin infusion), and alcohol discontinuation. TG levels will drop about 20-25% a day on this regimen. Plasmapheresis is sometimes needed. A fibrate or fish oil (or both) should then be added, and he should be advised to follow an American Heart Association diet (Chapter 10).

Our practice is to withhold TG-lowering medications until the serum TG level is <1000 mg/dl because, in our experience, people tend to ignore acute dietary modification in the belief that the medications will lower the TG level sufficiently. However, TG-lowering medications are ineffective when serum TG levels exceed 1000 mg/dl because the enzyme, lipoprotein lipase, is saturated at this level. The only currently effective intervention for serum TG levels above 1000 mg/dl is the approach described above.

30. A 26-year-old woman requests testing for thyroid cancer since her mother and two siblings have thyroid cancer. She notes headaches and palpitations for the past year. BP is 164/102. She has a 1-cm, left-sided thyroid nodule with no lymphadenopathy. Laboratory results: serum calcium = 11.2 mg/dL (nl, 8.5–10.5), phosphorus = 2.4 mg/dL (nl, 2.5–4.5), albumin = 4.5 g/dL (nl, 3.2–5.5), PTH = 55 pg/mL (nl, 11–54), calcitonin = 480 pg/mL (nl, 0–20), 24-hour urine metanephrines = 1,788 ug (nl, 0–400). Discuss her diagnosis and management.

The thyroid nodule, elevated serum calcitonin, and family history make medullary carcinoma of the thyroid (MCT) likely. Hypertension, headaches, palpitations, and high urinary metanephrines indicate a probable pheochromocytoma. She also has hyperparathyroidism. MEN type 2A (MEN2A) consists of MCT, pheochromocytoma, and hyperparathyroidism. It is an autosomal dominant syndrome that results from a germ-line mutation in the Ret gene. After alpha-blocker initiation and blood pressure control, treatment should consist of removal of the pheochromocytoma(s) followed by later removal of the abnormal thyroid and parathyroid glands. Screening at-risk family members for the Ret/MCT oncogene should also be performed (Chapters 43 and 60).

31. A 68-year-old man complains of progressive pain in the shins, knees, and left arm over the past 5 years. Physical examination: tenderness above the left elbow and enlarged bowed shins. Bone scan: intense uptake in both tibias and the left humerus. Skeletal x-rays: multiple lytic and sclerotic areas in the tibias and left humerus. Laboratory results: serum calcium = 9.8 mg/dL (nl, 8.5–10.5), alkaline phosphatase = 966 U/L (nl, 25–125). What is the probable diagnosis and what is the best treatment?

Bone pain and deformity and markedly elevated serum alkaline phosphatase levels suggest a diagnosis of Paget's disease. Intense radioisotope uptake on bone scanning supports this diagnosis and the characteristic findings on skeletal radiographs confirm it. Treatment options include analgesics, intravenous bisphosphonates (Zoledronic acid preferred), subcutaneous Denosumab, and Calcitonin. A single infusion of Zoledronic acid, 5 mg IV, will likely reduce symptoms and serum alkaline phosphatase levels for an extended period of time (Chapter 16).

32. A 19-year-old man has experienced fatigue, muscle weakness, and dizziness for the past 3 weeks. This morning he fainted during his morning run. BP 95/60, p 110. skin is cool, dry, and tanned. His thyroid feels normal. Lab Results: hematocrit = 36%, glucose = 62 mg/dL, sodium = 120 mmol/L, potassium = 6.7 mmol/L, creatinine = 1.4 mg/dL, blood urea nitrogen (BUN) = 36 mg/dL. What diagnosis do you suspect and how would you treat it?

Hyponatremia with hyperkalemia always suggests primary adrenal insufficiency. Fatigue, weakness, hypotension, tanned skin, anemia, azotemia, and hypoglycemia are consistent with this diagnosis. The most common cause is autoimmune destruction of the adrenal glands. The diagnosis is made by finding a basal serum cortisol level <3 ug/dl or by a Cosyntropin stimulation test showing no cortisol level of at least 18 ug/dl after ACTH administration. Measurement of 21 hydroxylase antibodies can establish an autoimmune etiology; if these antibodies are absent, adrenal gland imaging should be ordered.

During an adrenal crisis, however, one should not wait for these test results. If the diagnosis is suspected, one should draw a serum cortisol level (if a diagnosis is not already established) and start intravenous (IV) fluids and glucocorticoids. The recommended regimen for adrenal crisis is IV normal saline (1 liter over one hour, then guided by a clinical evaluation) and Hydrocortisone (Solu-Cortef) 100 mg IV immediately, then a 200 mg/24-hour infusion for 24 hours, followed by a 100 mg/24-hour infusion for 24 hours. Precipitating conditions should also be actively sought and treated. The patient should then be transitioned to an oral replacement regimen of glucocorticoids (Hydrocortisone or Prednisone) and, usually a mineralocorticoid (Fludrocortisone) (Chapter 36).

33. A 72-year-old woman is referred for hypercalcemia found on routine labs. She has had recent fatigue and "fuzzy thinking." PMH: GERD, Osteopenia. Meds: Ca Carbonate 2000 mg QD ("maybe more"). Vitals: BP 139/80, P 82. Physical exam: Normal. Further testing: Calcium 14.1 mg/dL, creatinine 7.1 mg/dL, CO_2 37 mEq/L, Phosphorus 2.7 mg/dL, PTH <1 pg/mL, PTHrP <1 pmol/L, 25 Vitamin D 35 ng/mL, Venous Ph 7.54. What is the most likely cause of her hypercalcemia and what is the best treatment?

Milk alkali syndrome features the diagnostic triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. It is caused by ingestion of excess calcium and absorbable alkali, most often calcium carbonate. Alkalosis occurs because the calcium-induced diuresis results in volume depletion, which stimulates renal bicarbonate absorption (contraction alkalosis). Treatment is hydration and stopping calcium, alkali, and vitamin D intake until the biochemical abnormalities resolve. Dialysis may be needed in some cases (Chapters 17 and 19).

34. A 38-year-old woman is referred for hyperthyroidism. She has recently been experiencing anxiety, fatigue, insomnia, thinning hair, and brittle nails. Medications: Vitamins, multiple Supplements. Vitals: BP 122/78, P 66. Physical exam: Thyroid normal, Eyes normal, Hair normal, Nails normal. Repeat evaluation: TSH 0.05 mU/L (nl: 0.45–4.5), Free T_4 3.6 ng/dL (nl: 0.8–1.8), trab positive, RAIU: 18%, Scan: Homogeneous Uptake. What is her likely diagnosis and best management?

She was asked about vitamins and supplements; her list included a hair and nail treatment that contained high amounts of biotin. She stopped the supplements temporarily and 3 days later her thyroid tests were normal. This is a case of biotin assay interference with results mimicking Graves' disease. Biotin is a component of the reagents for immunoassays of some hormones including TSH, T_4, T_3, and TRAB. People who take high-dose biotin supplements, a common OTC treatment for hair loss and brittle nails, can have falsely low serum TSH levels and falsely elevated serum T4, T3, and TRAB levels (in some assays) after high-dose biotin ingestion. Measurement of these hormones after at least an 8-hour (preferably 2–3 days) abstinence from biotin corrects this lab anomaly (Chapters 38 and 71).

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Sleep and Endocrinology

Roger A. Piepenbrink

> *"Our 24/7 society has led humans to be the only animal species that routinely ignores its biological clock as we are often awake when the clock is telling us to be asleep. Both the chronic disruption of circadian organization and chronic insufficient sleep [quality and quantity] have been associated with a wide range of mental and physical disorders. Modern medicine is only beginning to recognize that the treatment of many disorders of human health may need to take into account circadian medicine to improve overall 24-hour temporal organization between and within the central nervous system and peripheral tissues."*
>
> *–From Turek FW, Zee PC. Chapter 34 Master circadian clock and master circadian rhythm. In: Kyrger M, T Roth, WC Dement (eds) Principles and Practice of Sleep Medicine. 7th edition 2022, pages 351–353. Elsevier.*

In the 1300s, depending on location, between 30%–60% of the European population was killed by the plague. Since there was no treatment, the patients rapidly developed symptoms and died. A different type of plague is working its way through the United States; it starts insidiously for patients, sometimes in their youth, and kills more slowly. Such is the behavior of the plague of obesity, prediabetes (preDM), and type 2 diabetes mellitus (T2DM). It is estimated that over 30% of the US adult population over 20 years old already has preDM and by age 65 years and older nearly 60% of the population has contracted this plague. With time, 70% of people with preDM will progress to T2DM, the prevalence increasing in parallel with obesity.

This chapter explores the endocrine and sleep literature to highlight the metabolic contributions of sleep, e.g., sleep quality, quantity and even circadian disruption of sleep, to select endocrine metabolism and disease. Is it any wonder there is significant homeostatic interaction between sleep and endocrine function given that the major controllers for these two processes are co-located in the hypothalamus? Here, the 7 mm^3 hypothalamus is the integrative genius with the pituitary largely following its commands. As will be reviewed, anatomic proximity of neuroendocrine centers and sleep-wake centers in the hypothalamus foster functional integration to accomplish and protect homeostasis. This chapter will also cover normal sleep stages, the controllers for sleep and wake, human hormonal profiles as influenced by sleep-wake cycling, sleep deprivation and obstructive sleep apnea (OSA) with attention to governing neuroendocrine mechanisms. It will also cite improvements that result from successfully treating sleep abnormalities. Finishing this chapter will be some basics on how to obtain selected history and physical exam data germane to sleep disease.

1. Why should endocrinologists concern themselves with sleep wake cycles and circadian rhythmicity?

The 24-hour profile of nearly all pituitary hormones is related to the presence and quality of sleep. Stereotypical changes in nearly all hormonal and metabolic variables are observed surrounding sleep cycling and sleep-wake transitions. The absence of sleep, or the interruption of sleep, have potent influences on hormonal ebb and flow. This adds another layer of control to hormone release on top of the well-known feedback loops. Understanding these reproducible changes in view of sleep wake-cycling is fundamental to recognizing normal and early abnormal endocrine processes. For example, appreciation of normal hormone changes during the day and night provides insight into a patient's lab values drawn at varied times through a 24-hour period.

2. Do sleep disorders cause endocrine disease or does endocrine disease cause sleep disorders?

Both are true. Sleep experts have dubbed sleep symptoms as the “canary in the mine” for serious medical and psychological diseases. Sleep quality evaluation can be a tool for assessment of disease. Additionally, sleep disorders are common in many endocrine diseases. For example, acromegalic patients are at risk for sleep apnea (see Question 27). Excessive androgens can worsen OSA, as can hypothyroidism. Thyrotoxicosis can contribute to debilitating insomnia, with profound daytime fatigue accompanying other presenting complaints. Disruptive sleep is now known to be associated with increased risk for diabetes and shortened sleep is associated with obesity. Assessing the sleep habits of our patients is often omitted in pursuit of human pathophysiology. But sleep quality and quantity (i.e., sleep architecture) can be vital to anticipating components of disease.

3. What are the stages of human sleep?

Normal adult sleep is organized into rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep (e-Table 75.1), which is further divided into stages N1, N2, and N3. This final NREM stage is also called slow wave sleep (SWS). Each of these stages has specific electroencephalogram (EEG) characteristics. Typically, adults enter sleep through Stage N1. It usually takes 90–100 minutes for the first NREM sleep cycle to finish, but once completed it heralds the first REM period. Although REM is not defined by characteristic EEG patterns, the EEG can look like that of Stage 1. The hallmark of REM sleep is rapid movement of the eyes compared to the slow eye movements (SEM) seen on electrooculography (EOG) in Stage N1 sleep. Also defining REM is muscle atonia, manifest by the absence of chin muscle movement and attendant low electromyography (EMG) tone. The only somatic muscles working in REM are the extraocular muscles and the diaphragm! Curiously OSA, which can be predominant in REM, is associated with occult hyperglycemia. In SWS, the EEG slows and is associated with a progressive increase in the number of delta waves, which are characterized by increased amplitude and slowed frequency.

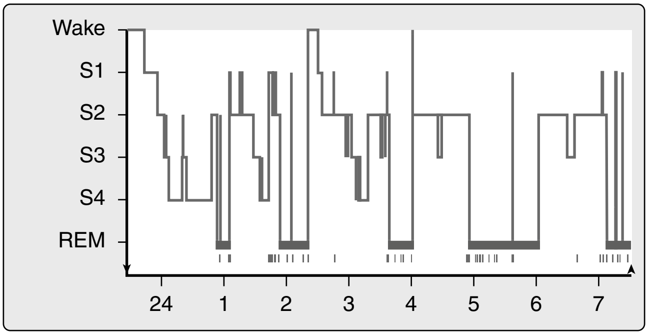
4. What is the progression of sleep stages in a usual night of sleep?

In the adult, NREM and REM sleep typically alternate in 90–120-minute cycles (e-Fig. 75.1). Four to five cycles occur during a normal sleep period depending on the length of sleep. Each cycle is identifiable with sleep onset initiating in Stage N1, progressing to Stage N2, then to SWS (N3), back through N2 and into REM. Once the individual achieves sleep, there is not a

E-TABLE 75.1 Comparison of sleep stages

CHARACTERISTICS	NREM	REM
responsiveness to stimuli	Reduced	reduced to absent
Sympathetic activity	Reduced	Reduced or variable
Parasympathetic activity	Increased	Markedly increased
Eye movements	SEMs	REMs
Heart rate	Bradycardia	Tachycardia/bradycardia
Respiratory rate	Decreased	Variable; apneas can occur
Muscle tone	Reduced	Markedly decreased
Upper airway muscle tone	Reduced	Moderately decreased to absent
Cerebral blood flow	Reduced	Markedly increased
Other characteristics	Sleep walk	Dreams
	Night terrors	

REMs, rapid eye movements; *SEMs*, slow eye movements.
Modified from: Chokroverty, S. (2006). Disorders of sleep. In Neurology (Chapter XIII). American College of Physicians Medicine, WebMD Inc.



e-Fig. 75.1 The progression of sleep stages across a single night in a normal young adult volunteer is illustrated in this sleep histogram. The text describes the ideal or average pattern. This histogram was drawn on the basis of continuous overnight recordings on electroencephalography, electrooculography, and electromyography in a normal 19-year-old man. The records were assessed in 30-second epochs for the various sleep stages. *REM*, Rapid eye movement. (Sullivan SS; Carskadon MA; Dement WC; Jackson CL. (2022). Normal human sleep: An overview. In M. Kryger, T. Roth, C. A. Goldstein W. C. Dement (Eds.). *Principles and Practice of Sleep Medicine*. (7th ed.). St. Louis, MO: Elsevier.)

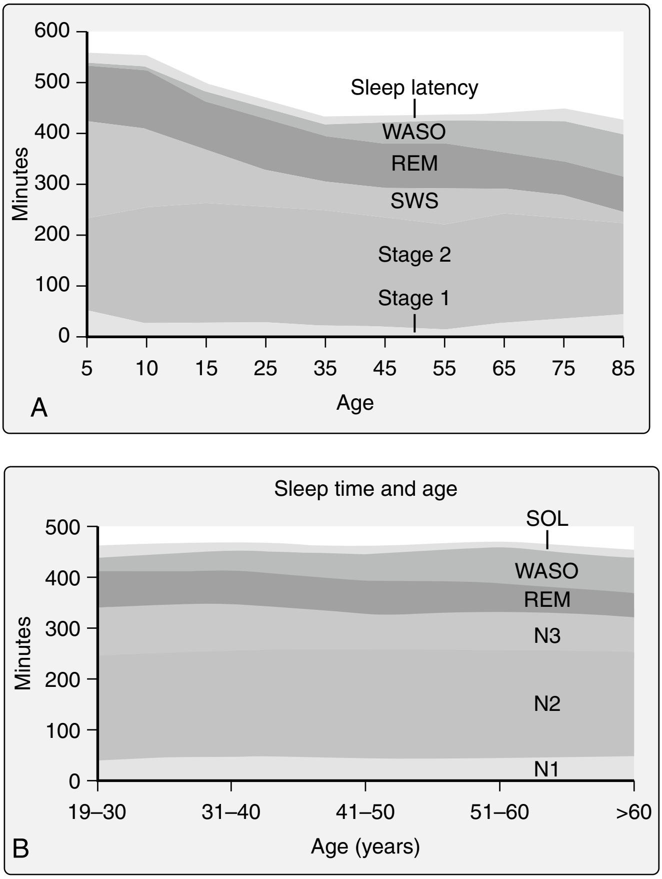
significant return to Stage N1. Therefore, once the adult sleep is underway, NREM sleep is largely N2 and N3. Sleep cycling can also be thought of as alternating between REM and SWS with N2 serving as a conduit between these two stages. In a typical night of adult sleep, Stage N1 will comprise up to 5% of total sleep, Stage N2 up to 50%, SWS up to 20%, and REM up to 25%. SWS is predominately experienced in the first third of a night of normal sleep and REM in the last half of sleep. Not achieving SWS or not achieving REM sleep has neuroendocrine significance. And for the individual, it is not just REM sleep, or just achieving SWS that confers restedness, but the full complement of >7 hours of 4–5 cycles with normal architecture that is critical to restorative sleep.

5. How do the sleep stages change during one's life span?

As we age, total sleep time decreases and sleep begins to fragment (e-Fig. 75.2). The time in sleep declines with age, from 16–18 hours a day in a newborn, to 9–10 hours in a 10 year old, to 7.5–8 hours in the average adult, and eventually to 6 hours in an 80 year old. A newborn's sleep is up to 50% REM sleep and this declines to 25% of sleep by adulthood. There is also a progressive decrease in SWS with aging. This change in sleep architecture also has endocrine repercussions since specific anterior pituitary hormone release is associated with particular sleep stages (see Question 15).

6. What are the fundamental changes in the nervous system in NREM versus REM sleep, and what other differences are noted between the phases of NREM and REM?

Widespread cortical slowing and autonomic nervous system (ANS) changes typify sleep (see e-Table 75.1). While awake, we interact with our environment, but when asleep we are largely unresponsive to sensory input and do not generate motor output. During NREM, EEG activity is slower and of higher voltage than when awake, and blood flow is decreased. During REM sleep, the cortex is activated, EEG is similar to wakefulness, and blood flow is increased. There are also changes in the ANS during sleep, with parasympathetic nervous system (PNS) predominance in NREM and even more so in REM. Sympathetic nervous system (SNS) tone decreases in NREM and usually in REM, but PNS and SNS tone can be variable during REM. In NREM, there are decreases in respiratory rate (RR), heart rate (HR), blood pressure (BP), and cardiac output. Normal REM is characterized by fluctuations in BP, HR, and RR. Dreaming and somatic muscle hypotonia to atonia, which includes reduced to absent upper airway muscle tone, are also characteristic REM events. REM may have a few periods of decreased or absent breathing. Cerebral metabolic rates for glucose and oxygen decrease during NREM, but *increase to above waking levels* in REM. As mentioned, REM-predominant OSA can be associated with hyperglycemia (preDM and T2DM).



e-Fig. 75.2 Changes in sleep with age. (**A**) Time (in minutes) for sleep latency and waking after sleep onset (WASO) and for rapid eye movement (REM) sleep and non-REM (NREM) sleep stages 1, 2, and slow-wave sleep (SWS). Summary values are given for ages 5 to 85 years. (B) Changes in sleep in adults using the current American Academy of Sleep Medicine (AASM) scoring standards. Time (in minutes) for sleep latency and WASO and for REM sleep and NREM sleep stages N1, N2, and N3. Values are medians. From Carskadon, M. A., Goldstein, C. A. & Dement, W. C. (2022). Normal human sleep: An overview. In M. Kryger, T. Roth, W. C. Dement (Eds.). Principles and practice of sleep medicine. (7th ed.). St. Louis, MO: Elsevier; (A) From Ohayon, M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep, 27, 1255–1273; (**B**) Data from Mitterling, T., Högl, B., Schönwald, S. V., Hackner, H., Gabelia, D., Biermayr, M., & Frauscher, B. (2015). Sleep and respiration in 100 healthy Caucasian sleepers—a polysomnographic study according to American Academy of Sleep Medicine standards. *Sleep*, 38, 867–875.

7. What are the systems and neurotransmitters responsible for wakefulness and for the sleep state?

Our contemporary understanding of the endocrine system includes much more neuroendocrinology. The discussion in this chapter highlights the interactions among the cortex, brain stem, hypothalamus and pituitary. Central nervous system (CNS) accomplishment of sleep-wake changes can be best modeled as flip switches, where neural networks responsible for either state are mutually inhibitory, i.e., when one is active, there is inhibition of the other. If the sleep network is active, then the wakefulness network is inhibited. Importantly, sleep is accomplished through the inhibitory influence of primarily one neurotransmitter on the arousal centers, while wakefulness is promoted by an arousal system that relies on several neurotransmitters. Transition to sleep is accomplished through wake-inhibiting neurons primarily localized to ventrolateral preoptic (VLPO) nuclei and mediated primarily through the inhibitory neurotransmitter γ-aminobutyric acid (GABA). So the transition from wake to sleep is mediated through the release of GABA from VLPO nuclei, inhibiting the arousal system and thalamocortical association. If this arousal system, the so-called reticular activating system (RAS), is inhibited, sleep is promoted. Conceptually, sleep control is subdivided into sleep switches with NREM switches governing NREM sleep and REM switches governing REM sleep. During NREM sleep, forebrain NREM-on neurons are firing; during REM sleep, REM-on neurons are firing. In turn, when transitioning from sleep to wake, the brainstem RAS inhibits the VLPO nuclei. The brainstem RAS has a series of cortical activating nuclei with different neurotransmitters: norepinephrine, acetylcholine, serotonin, dopamine, and histamine. This RAS, also known as the ascending reticular activating system (ARAS), projects to the cortex. Dorsal and ventral routes of the RAS have been identified. The dorsal route is composed of ascending projections through the thalamus to the cortex; the ventral route projects to the posterior hypothalamus and basal forebrain (BF). This ventral route receives inputs from the melanin-hypocretin (orexin) concentrating neurons in the lateral hypothalamus or cholinergic neurons of the BF. There are also RAS projections down the spinal cord for muscular tone and postural control. Even though these tiny tufts of neurons with their respective neurotransmitters are known as specific nuclei, their visualization evades current clinical imaging techniques.

8. What are the two basic processes controlling sleep timing and sleep quality and therefore contributing to anterior pituitary hormone cycling in a 24-hour period?

The following should serve as a framework for understating these two time-honored processes. For more in-depth rendering, please see selected references. **The first process** is called *Process-C*, for circadian process (*circadian* from Latin "approximately a day") and is regulated by the hypothalamic suprachiasmatic nuclei (SCN). This nucleus receives input from environmental cues, the strongest of which is light. Process-C is the broader of the two processes and transmits circadian output to coordinate behavioral, physiological, and genetic rhythms. **The second process** is Sleep-Wake Homeostasis (SWH), also known as *Process-S*. SWH is dependent on Process-C, but the circadian process is not dependent on SWH. SWH is presently conceptualized as a process relating the amount and intensity of sleep to the duration of prior wakefulness. SWH, not having specific anatomic localization, is better thought of as an adenosine system with wakefulness accumulating adenosine and directly influencing sleep pressure. So, if one has 24 hours with no sleep, there is increased pressure to sleep. The pressure to sleep is least when most rested. This pressure increases during the day and peaks just before midnight. The continuous interaction of these two processes, Process-C and Process-S, influence the hypothalamic generators of releasing or inhibiting hormones from the anterior pituitary, which in turn contributes to the 24-hour hormone profile.

9. Discuss the basic mechanisms of Process-C

Research has uncovered *core molecular clock* machinery responsive to Process-C in most tissues! The bilateral or paired SCN of the hypothalamus are regarded as *the sole* master 24-hour pacemaker. Research has shown the circadian process to be a *hierarchy* of oscillations starting with oscillations from the SCN centrally emanating to the periphery, i.e., downstream oscillations within the brain and then to peripheral tissues. Interactions between several hypothalamic nuclei are also involved in Process-C. Importantly, SCN timing is genetically determined to be slightly >24 hours and must be modified or reset (synchronized) to the 24-hour day–night cycle by environmental stimuli (*zeitgebers*, German for, "time givers" or "time cues"). The brain is employing these mechanisms to adjust to and optimize systematic function according to the location of the body.

10. How is the circadian system organized?

Using engineering parlance, the organization of the circadian system consists of three parts: (1) input system, (2) oscillator network, and (3) output system. The *input system is* represented by the retinal hypothalamic tract (RHT). The *oscillatory network*, itself with 3 parts, is represented by SCN entrainment and tissue oscillators. The *output system* is represented by tissue-specific peripheral circadian outputs. For example, circadian outputs of muscle could be glucose uptake and oxidation; in the liver, they could be glucose uptake and production; in adipose tissue, the circadian outputs are lipolysis and lipogenesis; and in the pancreas, they are insulin and glucagon secretion. In fact, through different experimental sources, epidemiological, clinical, and especially mammalian genetic study techniques, recent work, has demonstrated exciting links of circadian disruption with T2DM pathophysiology and its treatment.

11. How does the circadian input system, i.e., the RHT, work?

Photic information is transmitted from the retina directly to the oscillator network in the SCN via the RHT. But the photic information is not communicated by retinal rod and cone cells. *Within the retinal* there are nonrod, noncone cells, the so-called retina ganglion cells (RGC). These cells contain a photopigment, melanopsin, which is preferentially excited by the short wavelengths, especially blue light. *The RGC/RHT system then can be thought of as a transducer and tract, respectively, for communication of light-dark (LD) information to the SCN.* Normally the SCN is most active during the day and most inactive at night. SCN activity inhibits the tonic activity of the paraventricular hypothalamic (PVH) nuclei, which normally is a stimulus for melatonin synthesis from the pineal. So, by SCN inhibition of the PVH, daytime melatonin production decreases. In the absence of light, the PVH stimulates the pineal gland to allow melatonin secretion. It would be easier to understand if the RHT went directly to the pineal gland. But this would omit levels of integration which are associated with this melanopsin-RHT signal. This chemical LD signal is not just destined for the pineal gland; it also reaches non-SCN circadian centers as well as sleep-wake centers.

12. Since the circadian oscillatory network has 3 components (SCN, entrainment, and tissue oscillators), what is the basic SCN organization and the basic molecular mechanisms of the circadian clock systems?

The SCN cytoarchitecture reveals functional organization. In mammals, the SCN is comprised of some 100,000 neurons and is divided into a primarily light-sensitive *SCN core*, which receives the unique nonimage retinal input (RGC/RHT), and a *SCN shell*, which is capable of generating rhythms. As will now be discussed, these central and peripheral circadian oscillations have very similar genetic processes.

Modern lab techniques in tissue cultures and genetics are allowing real-time monitoring of circadian rhythms. The transcriptional and translational processes interact in feedback loop relationships, constantly running in nearly every cell of the body, and are regulated to a 24-hour cycle with periods of activity and quiescence. Importantly, if SCN cells are removed from the body or are placed in complete darkness, they are still capable of maintaining a 24-hour period of activity, despite the absence of an external LD cue. This molecular clockwork, as the experts call it, has two primary positive loop genes, *circadian locomotor output cycles kaput (CLOCK)* and *brain and muscle ayrl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1).* Usually at the start of the day these two proteins, CLOCK and BMAL1, will noncovalently join (heterodimerize) and, through a complicated series of events, this heterodimer will activate transcription of negative feedback signals. These negative loop components typically are *periodic circadian protein* (PER1 and PER2) and *cryptochrome* (CRY1 and CRY2). The PER and CRY proteins, in turn, heterodimerize and repress BMAL1-CLOCK activity. The nuclear receptors *Rev-erb* α/β and *ROR* α/β are also involved in control and stabilization of this system, as they act as transcriptional repressors and activators, respectively, of BMAL1. Up to 20% of the cells studied use this same genetic method of regulation; specifically included are the regulation of transcription, translation, and mRNA processing (formation, degradation, micro-turnover, and splicing). The oscillations are independent of retinal input, and destruction of the SCN abolishes oscillations with significant downstream influence (e.g., certain behaviors, such as drinking and movement; and hormonal rhythms, such as cortisol).

13. Based on the description of the circadian system, elaborate on its second part, “entrainment” and how is it related to “synchronization” of circadian rhythms

Circadian rhythms are synchronized to the 24-hour day through the process of entrainment. As outlined above, the SCN is the neural pacemaker for biological rhythms, but is set at >24 hours. Entrainment of the SCN to daily stimuli is the interpretation of environmental cycle information, which then allows for adjustment of the intrinsic period of the pacemaker to the environment. Light is the dominant correcting factor or time cue, capable of inducing sleep phase or wake phase changes. Besides light, nonphotic cues like exercise, social interaction, temperature changes, and feeding also help entrain circadian rhythms.

The interaction between photic and nonphotic clues is complex and the magnitude of contributions to the human system remains to be determined. At this point, it can be said that stable entrainment likely reflects integration of both central and peripheral parameters.

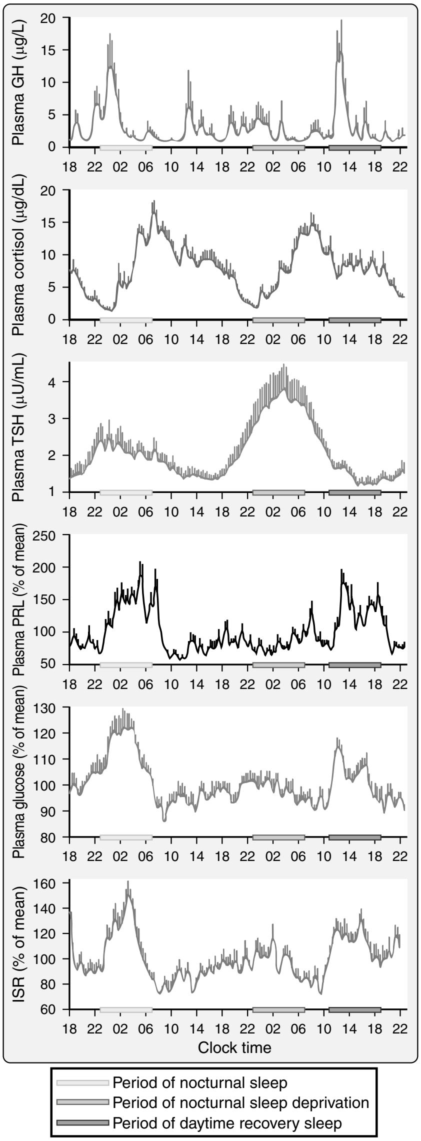
14. How is melatonin involved in regulation of circadian rhythms and are there any other hormones that contribute to circadian rhythm regulation?

Melatonin communicates a chemical message of light-dark cycling (LD cycling) peripherally, that is, *to the remainder of the body*. Melatonin levels are involved in synchronization of circadian rhythms through a circuitous neural communication to the SCN and periphery. As mentioned, the intrinsic circadian rhythm from neuronal activity in the SCN is slightly >24 hours; therefore, the SCN clock must be reset daily by extrinsic time cues, most importantly the LD cycle. The SCN projects into the PVH, mediating melatonin synthesis. Melatonin levels in the pineal gland are inhibited by light and increase at sundown, peaking at mid-darkness. This makes the neurohormone, melatonin, the chemical message communicating photoperiod “fine tuning” to the autonomous master clock in the SCN. This communication occurs through specific melatonin receptors. The MT1 and MT2 melatonin receptors are G-protein coupled with characteristic seven transmembrane domains. These two melatonin-receptor families are distributed throughout the brain (including the SCN itself) and in peripheral tissues, such as adipocytes, macrophages, platelets, gastrointestinal tract, liver, heart, kidneys, and adrenal glands. The melatonin *receptors are only receptive at the light-dark transitions*, and thus exogenous administration of melatonin is most effective at these transitions. Therefore, pineal circadian melatonin production results from direct neuronal input from the SCN and can be regarded as hormonal output from the central circadian clock.

The glucocorticoid (GC) hormone profile joins melatonin as a major modulator of the circadian rhythm, which then confers time-giving properties from central to peripheral clocks. In contrast to other endocrine end-organ hormones (e.g., fT4 and IGF-1), which remain generally stable, the blood concentration of GCs oscillates through a 24-hour periodicity and shorter periods (ultradian) for needed episodic release. The former provides “gearing up” for the anticipated needs of the body, while the latter is episodically called out in rapid response to stressful stimuli. The major external synchronizer for the SCN master clock is ambient light, with melatonin regarded as hormonal output from the CENTRAL (i.e., SCN) circadian clock. It is the central SCN clock that governs normal CRH secretion, which then governs pituitary ACTH release and the attendant GC secretion from adrenal cortex. This normal release pathway, CRF→ACTH→GC ultimately works through the glucocorticoid receptor (GR). But the master SCN circadian clock does not express GR in significant amounts and thus it is not sensitive to the 24-hour CG changes nor episodic CG changes. It follows then that adrenalectomy has little influence on SCN circadian gene expression. Yet given the ubiquitous somatic distribution of GR, circadian GC release becomes the synchronizer of the central clocks with somatic peripheral clocks. Molecular feedback loops generating central and now peripheral circadian rhythmicity work through the CLOCK and BMAL1, positive feedback loop, which includes CRY and PER genes that can inhibit their own CLOCK/BMAL1 translocation, constituting a primary negative feedback loop (see Question 12). The key hypothalamic nuclei, including the PVH (stress response, sympathetic tone modulation) and arcuate nucleus (hunger, appetite feeding modulation) have a generous distribution of GR, which allow for synchronization of non-SCN brain clocks with the 24-hour GC profile.

15. Name the two hormones elevated early in sleep and the two hormones elevated late in sleep

Recall that SWS predominates during the first third of sleep and REM predominates during the last half of sleep. Growth hormone (GH) and prolactin (PRL) are entrained to SWS (e-Fig. 75.3). The increase in GH secretion during sleep is well known. Regardless of age and gender, most PRL secretion also occurs when the individual is asleep, with nocturnal maximum PRL levels being twice that of daytime levels. The nighttime GH and PRL surges are associated with the first period of SWS. In fact, the GH surge immediately after sleep onset is the largest of the 24-hour period for both genders, though females burst less than males. Females have two evening GH bursts; the first is before sleep onset and a second occurs with SWS. Males have few daytime GH pulses compared to females. The surges of PRL and GH are lost if a person goes sleepless and



e-Fig. 75.3 Mean 24-hour profiles of plasma growth hormone (GH), cortisol, thyrotropin (thyroid-stimulating hormone [TSH]), prolactin (PRL), glucose, and insulin secretion rates in a group of eight healthy young men (age 20–27 years) studied during a 53-hour period including 8 hours of nocturnal sleep, 28 hours of sleep deprivation, and 8 hours of daytime sleep. The vertical bars on the tracings represent the standard error of the mean (SEM) at each time point. The horizontal bars are the following periods: light gray is nighttime sleep, medium gray is nocturnal sleep deprivation, and darkest gray is daytime recovery sleep. Caloric intake was exclusively under the form of a constant glucose infusion and the subjects remained recumbent throughout the study period. Shifted sleep was associated with an immediate shift of GH and PRL release. In contrast, the secretory profiles of cortisol and TSH remained synchronized to circadian time. Both sleep-dependent and circadian inputs can be recognized in the profiles of glucose and Insulin Secretion Rate. From Hanlon E.C.; Van Cauter E.; Tasali E.; Broussard J.L. Chapter 27. Endocrine physiology and relationship to sleep and sleep disturbances. In M. Kryger, T. Roth, C. A. Goldstein, W. C. Dement (Eds.), 2022 Principles and Practice of Sleep Medicine. (7th ed.). Philadelphia: Elsevier Saunders.

return if the person gets recovery sleep. *It is the onset of sleep and not the time of day that triggers GH release while PRL also has a strong circadian trigger.*

The hormones that increase later in sleep are testosterone and cortisol. Testosterone rises just after midnight and cortisol begins its rise at 2 AM, peaking 6–9 AM. The timing and amount of REM sleep are related to the late-sleep rise of these two hormones in men. But the 24-hour rhythm for both testosterone and cortisol is primarily controlled by circadian rhythmicity (Process-C) and not sleep-wake homeostasis (Process-S). Before we leave this subject, it is well known many drugs increase serum prolactin levels (e.g., narcotics, antiemetics, antipsychotics). Added to this list are the benzodiazepine sedatives and imidazopiridine hypnotics, such as triazolam and zolpidem. Taking either at bedtime is associated with nocturnal, but not daytime, marked increases in serum prolactin.

16. How does gonadotropin release change from youth to adulthood, and is the LH adulthood pattern solely responsible for gonadal steroid release?

Regarding changes to maturity: Sexual maturity is geared to enable men and women to achieve daily sperm and monthly egg production, respectively. There is a pulsatile release of both LH and FSH before puberty and increased pulses occur with sleep. Gonadotropin secretion during the day is without circadian rhythm, differing from testosterone, which has a significant circadian rhythm. The gender-similar gonadotropin patterns diverge with puberty, with the menstrual cycle phase exerting unique influences on LH pulses. Indeed, *one of the hallmarks of puberty is increased nocturnal pulse amplitudes of LH and FSH.* Each LH pulse is in direct response to a hypothalamic gonadotrophin releasing hormone (GnRH) surge. However, GnRH pulses are not directly related to pituitary FSH secretion. With the advent of sexual maturity, the brisk LH and FSH pulses of puberty give way to lower amplitude, 90-minute interval LH bursts without significant diurnal variation. Essentially the male will continue his 90-minute interval LH pulses with little FSH pulsatility, while the female will show marked increases of LH pulse frequency during the follicular phase, with little change to the amplitude in either the follicular or luteal phases. There is a nocturnal LH pulse frequency decrease in the early follicular phase but not in the luteal phase. This slowing is sleep-wake related and is not circadian (i.e., seen in day-time sleep but not seen in night-time wakefulness). Finally, FSH and LH secretion are increased in men and women as they age, with pulse frequency being increased while amplitude is decreased. Additionally, in men age 30 years and onward there is a progressive decline in total testosterone associated with an increase in sex hormone binding globulin, resulting in an even greater decline in serum free testosterone levels; for this reason, free or bioavailable testosterone measurements may be warranted when evaluating older men for hypogonadism. The serum gonadotropin rise and pulse frequency increase are noted in menstruating women >40 years old. One study showed a causal relationship between gonadotropin elevation, vasomotor symptoms (VMS), and decreases in objective and subjective sleep quality. The North American Menopause Society published a 2017 position statement regarding the use of menopausal hormone replacement therapy (HRT). Therein it is noted that the benefit-risk ratios for HRT are most favorable for women who are <60 years old or who are within 10 years of the start of menopause, and who have no contraindications for HRT treatment of bothersome VMS and for those at elevated risk for bone loss or fracture.

- **Regarding gonad steroid release:** FSH stimulates recruitment and growth of immature ovarian follicles and preservation of growing follicles in females. Once a follicle is in the 8–10 mm range, its estradiol secretion markedly increases. Mean monthly estrogen is essentially constant in eumenorrheic females, yet a diurnal free estradiol rhythm exists and consists of two major components: (1) an asymmetrically peaked diurnal cycle and (2) ultradian (shorter than a day) harmonics in the range of 6–12 hours. The diurnal and ultradian rhythms are remarkably consistent throughout the menstrual cycle in terms of 24-hour mean level, peak width and amplitude. In contrast, there is less complicated diurnal variation in males. The early morning rise in testosterone that started at sleep onset, increases to maximum levels during the last half of sleep (REM predominant) and is not associated with corresponding LH surges. The characteristic male nighttime LH bursts occur later on, during the last half of sleep. Recently, a testosterone surge was observed during adult day-time recovery sleep, and a testosterone decrease followed as the patient remained awake after this day-time recovery sleep. All this suggests that sleep itself, independent of LH bursts, contributes to testosterone release. Therefore, *the 24-hour testosterone profile and its response to sleep deprivation and daytime recovery sleep are more like the prolactin profile* (e-Fig. 75.3).
- **Tying this together using an example:** When a sleep-deprived male internal medicine resident finally gets some sleep, his testosterone will surge during recovery sleep; remember that during the usual day for one who has not slept, testosterone levels are on a decline. So, if

low testosterone is found in an individual, it may be from primary hypogonadism, but it may also be sleep deprivation, OSA or even shift work. For the female shift worker, they will have the typical fragmented and shorter sleep, but the oft-times associated menstrual irregularities could be from the altered sleep patterns. *But in both genders with normal sleep-wake cycles there is no significant circadian pacemaker for the gonadotropins' diurnal change.* It is fair to tell our patients to get their testosterone levels drawn first thing in the morning in a rested state, based on the observations that sleep increases testosterone, wakefulness decreases it, and the circadian influence may be less potent than sleep-wake homeostasis.

17. What are the sleep characteristics associated with rising AM testosterone levels?

There is accumulating evidence in adult men that the testosterone profile is significantly influenced by NREM-REM cycling. Sleep architecture and characteristics which are associated with a nocturnal rise in AM testosterone are the following: (1) duration of the first NREM period; (2) daytime recovery sleep; and (3) habitual sleep duration. Restriction of sleep to 5 hours/night for just 5 consecutive nights decreases AM serum testosterone levels up to 15% and one night with no sleep or sleeping only 4.5 hours in the first half of the night decreases AM testosterone levels by 20%. *These facts argue for assessing sleep habits of our patients in the workup for hypogonadism (see last question of the chapter on taking sleep history).*

18. Does penile tumescence have any relation to sleep architecture, and if so, what?

Since the 1970s it has been known that nocturnal erections are phenomena of REM sleep. Therefore, the classic hypogonadal teaching that decreased morning erections are due to low testosterone levels may be related to more than one primary problem. The patient with decreased or absent morning erections may have hypogonadism, but the root cause could lie in abnormal sleep architecture (i.e., sleep disease impairing REM density). One recent 12-week randomized trial evaluated the use of CPAP vs vardenafil vs placebo in a two-by-two factorial study design in 61 men (mean age 55 years old, BMI 32kg/M2) with AM serum total testosterone levels ≤299.9 ng/dl. The CPAP treatment groups showed improvement in, among other parameters, nocturnal erections. The use of CPAP for 6.2 hours per night resulted in a decrease in respiratory events from a mean apnea-hypopnea index (AHI) of 39 events to 14 events per hour in the per-protocol group. Note that CPAP, in this study, improved OSA from the severe range to the mild range but not into the normal range (AHI <5 events/hour). One might speculate that even better results would be seen with normalized breathing (AHI <5 events/hour) at night. Regardless, the authors conclude "these data may convince some men who highly value erectile function to adhere to CPAP therapy." Other endocrine systems also show a dose-duration response improvement with CPAP. Another inference from these data supports closer historical screening for sleep disease (see Question 42) in those patients admitting to decreased or absent morning erections.

19. Is the testosterone decline observed with aging related to changes associated with the sleep pattern of aging? Yes, at least in part.

As discussed previously (e-Fig. 75.2), aging is associated with less time in overall sleep and less time in SWS. In older men, LH pulses show lower amplitude but increased frequency (see Question 16 for a more complete answer). Also, to this author's knowledge, not all the parameters listed in Question 17 above have been considered and, therefore, could be confounders to the data associated with testosterone changes in aging. The sleep-related testosterone rise is still seen in older men, though the magnitude is less, and it is no longer associated with duration of the first NREM period.

20. What factors influence thyroid stimulating hormone release?

Thyroid stimulating hormone (TSH) secretion is primarily related to the circadian rhythm, Process-C, though there is also Process-S influence (i.e., sleep wake homeostasis - SWH). TSH secretion in young healthy males shows an early evening circadian elevation before sleep onset, then a decline shortly after sleep onset continuing until it reaches a nadir in the afternoon. The inhibitory influence of sleep on TSH release is thought to occur during SWS. Therefore, clinicians may need to temper therapeutic decisions made on the basis of a sole mid-afternoon TSH value or an evening TSH level ordered in an emergency department. The highest TSH levels in the daytime, when our outpatient labs are open, are after a person wakes up. With acute sleep loss, TSH takes its usual early evening upturn at approximately 6 pm but instead of the usual TSH downturn at sleep onset, with sleep deprivation TSH continues to rise to nearly twice the normal maximum through the middle of the usual sleep period. TSH hits a peak in the mid total sleep deprivation period and from there begins a downward trajectory, eventually normalizing in the sleep-deprived individual's day-time recovery sleep. Thus, a TSH value obtained at 7 am in such a patient reflects the influence of lack of sleep and probably does not reflect the need for thyroid hormone initiation or adjustment. The loss of an inhibitory effect of sleep on the circadian TSH elevation may contribute to elevated TSH values seen in acutely ill hospitalized patients.

21. Since TSH and cortisol secretion profiles are circadian, why are their levels not parallel through the night and day?

The difference in these two hormone profiles is attributable to the extent that each is influenced by either Process–C or Process-S (e-Table 75.2). However, this question is not straightforward. The difference demonstrates nicely the primary Process-C contribution to cortisol secretion versus the influence of a combination of Process-S plus Process-C on TSH secretion. In general, the day-to-night pattern for both hormones is not parallel, but they are similar (e-Fig. 75.3). The patterns of both reveal the highest hormone levels during sleep and the lowest levels during the day, but the 24-hour highest level for TSH occurs as a person goes to sleep, while the cortisol peak occurs as the person wakes up. The cortisol profile is nearly all circadian-governed (Process-C), so it does not show significant variation with acute sleep deprivation. In contrast, nocturnal TSH will *increase* with acute sleep loss and *decrease* with daytime-recovery sleep. Thus, the evening TSH increase before sleep onset reveals Process-C influence, while the decrease of TSH during sleep reflects an influence of Process-S. To continue a description of the excursion of these hormones during a normal 24-hour cycle, TSH fluctuations precede those of cortisol, with *TSH starting its rise before sleep onset* and before the cortisol rise and starting its descent also before the cortisol descent. Cortisol peaks in the last third of the night, and, as mentioned, TSH begins to rise before sleep onset. Then, with sleep achieved, TSH hits its peak between 10 pm and midnight followed by a slow during-the-day TSH decline with a nadir by mid-afternoon. Given that corticotrophin (ACTH) release is primarily influenced by the time of day (Process-C), the normal 24-hour cortisol profile does not have a significant change in shape with total sleep deprivation or during daytime recovery sleep. Cortisol will hit its 24-hour nadir after the transition to sleep, between 10 pm and midnight; then, as though someone rattles its cage, cortisol rises abruptly after midnight and peaks at 6–9 am (by the 2nd third of sleep, the cortisol rise is underway regardless of sleep-wake state). Normal awakening is the herald of the cortisol decline, progressing over the entire waking period with a nadir after sleep transition in the successive night of sleep. But as the reader knows, cortisol is a stress response hormone and will increase with stress (e.g., someone pulls in front of you inappropriately, or there is a morning dentist drilling planned); with such events, this end-of-the night-start-of-the-day burst of cortisol pattern will change. This stress-sensitive trigger is not seen with TSH. *Therefore, a change to one's sleep-wake cycle influences the release of both hormones but to different extents.* In a study of healthy young men during nocturnal sleep deprivation from 10 pm to 6 am, with the lack of TSH suppression by sleep, TSH more than doubled. That is, TSH rose from its afternoon nadir of approximately 1.5 mU/L to a new peak of approximately 3.8 mU/L at 2 am and, in the follow-on recovery sleep (10 am–6 pm), TSH returned to a mean of 1.25 mU/L; but there was no effect on cortisol. It is well documented that interruptions

E-TABLE 75.2 Primary influence on 24-hour variation

HORMONE	SLEEP–WAKE HOMEOSTASIS	CIRCADIAN
GH	+++	+
PRL	+++	++
TSH	v+	+++
Testosterone	++	++
Cortisol	+	+++

GH, Growth hormone; *PRL*, prolactin; *TSH*, thyroid-stimulating hormone.

to nocturnal sleep are associated with short-term TSH elevations. TSH levels normalize when normal nocturnal sleep is resumed. In contrast to the absence of acute sleep deprivation effects on cortisol, repeated and prolonged nocturnal sleep interruptions do result in cortisol elevations.

22. Jet lag is not uncommon. How are some of its symptoms attributable to the observed changes in cortisol and TSH?

Jet lag is known as a sleep disorder arising from crossing multiple time zones in a short period of time. However, it probably has underlying endocrine pathophysiology. Essentially, the circadian process becomes misaligned with the destination time zone. This is particularly true when flying east, which moves time zones ahead and puts the individual at risk for insomnia, while flying west moves the time zones back, putting the traveler at risk for daytime sleepiness in the new time zone. For example, if a physician departs London on a nonstop flight of 10 hours west to Los Angeles (LA), the doctor's circadian clock is set to London although her/his body is now located in LA. London is 8 hours ahead of LA. So, if the flight leaves London at 8 am, he/she will arrive in LA at 6 pm London time (in her/his circadian clock); but because of the 8-hour time difference, it is 10 am Pacific Standard Time (PST). He/she clears customs, luggage in tow, and by noon is at home and is exhausted. She/he sleeps 8 hours and wakes at 8 pm PST. You can see that this person will struggle with unwanted sleepiness and insomnia until his/her clock shifts from London time to PST. This is even more pronounced when flying east, which moves the clock ahead and puts the individual at greater risk for insomnia.

Insomnia patients, whose total time asleep/total time in bed is less than 70% of normal, have significantly higher evening and early sleep cortisol levels. In a study of young adults whose circadian rhythms were perturbed by a flight from Europe to the United States, *GH secretory patterns adjusted within a few days to the new sleep-wake cycle, but the cortisol levels remained disassociated for two weeks*. This dissociation is thought to contribute to the symptoms of jet lag syndrome. Disruption of the hypothalamic-pituitary-thyroid axis during prolonged flight has also been studied. The usual TSH-suppressive influence of sleep may not be present in prolonged air travel as the traveler remains awake. This translates to an overall TSH elevation, paralleled by a small, temporary increase in serum T3 levels. The study related the fatigue and discomfort of jet lag syndrome to the prolonged elevation of thyroid hormone as well as to the desynchronization of multiple circadian rhythms.

23. How do circadian and sleep-wake processes influence glucose and insulin levels?

Glucose and insulin levels are influenced by both Process-C and SWH. Studies in normal adults have demonstrated a 30% increase in glucose and a 60% increase in insulin levels during nocturnal sleep. During sleep deprivation, glucose levels and insulin secretion rates increase at the habitual sleep time, though to a much lesser degree, suggesting circadian modulation. In recovery sleep, however, glucose levels and insulin secretion both markedly increase, suggesting modulation by sleep itself.

In a recent review, evidence was presented suggesting that multiple processes within adipose tissue (e.g., inflammatory pathways, lipogenesis, lipolysis, and even insulin sensitivity, etc.) are controlled by the circadian clock; furthermore, with clock disruption, there is enhanced adiposity, insulin resistance, and increased susceptibility to type 2 diabetes development. Finally, compelling evidence was presented highlighting how circadian clocks contribute to islet cell function, having a critical role in the regulation of beta cell, and alpha-cell function and turnover. With regard to therapeutic targeting, as mentioned in Question 14, *melatonin can be regarded as hormonal output from the central circadian clock*. Timed melatonin supplementation in rodents has been shown to reduce adiposity while also decreasing skeletal muscle and hepatic insulin resistance. In addition, islet cells from type 2 diabetic subjects isolated in cell culture showed improved glucose-stimulated insulin secretion and beta cell survival in response to melatonin. The highlighted mechanisms included attenuation of induction of oxidative and endoplasmic reticulum stress.

24. How does aging change hormonal release?

Changes to sleep architecture with aging are thought to lead to hormonal changes. Normal aging is associated with loss of SWS and REM, with increased sleep fragmentation (see e-Fig. 75.2). Recall that GH and PRL rise primarily in relation to the SWS of NREM, whereas TSH, cortisol, and testosterone increases are primarily under circadian control. In younger men, there is a dose response relationship between SWS and GH secretion. For example, in 16–25-year-old males SWS is nearly 20% of the sleep period and tails off to 5%–10% at age >40 years. This is associated with GH secretion during sleep of ~350 ug in the 16–25 year old, but not more than 100 ug in individuals >35 year old. Most of the PRL released during a 24-hour period is during sleep regardless of gender; there is nearly a 50% decrement in nocturnal PRL secretion with aging. The extent of circadian changes in cortisol and TSH are less dramatic with aging. Day–night TSH fluctuations also dampen with age.

25. What is the definition of sleep disordered breathing (SDB) and how does this differ from obstructive sleep apnea?

Confusion arises when the terms sleep disordered breathing (SDB) or sleep related breathing disorders (SRBD), and OSA are used interchangeably in the literature and in sleep lab reports. SRBD and SDB are disease headings under which other diseases are arranged, much like COPD comprises a general reference for other specific pulmonary disease entities. SRBD on the one hand contains adult and pediatric central sleep apnea and OSA syndromes. OSA, on the other hand, is a specific adult and pediatric disorder that is diagnosed with polysomnography (PSG). OSA can be suspected on the basis of patient or bed partner complaints. Such complaints include: unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, waking from sleep with breath holding, gasping or choking, loud snoring, and breathing interruptions. Rendering the diagnosis of OSA includes ruling out current medical, neurological, and/or substance abuse disorders. Of note, some prescribed medications can also increase the risk for OSA.

26. What are respiratory events?

Respiratory events are apneas, hypopneas and respiratory effort-related arousals (RERA). An apneic episode is an airflow decrease of at least 90% from baseline lasting at least 10 seconds (try holding your own breath for 10 seconds!). Hypopnea is defined as 10 seconds of at least a 30% decrease in airflow, resulting in ≥4% desaturation on pulse oximetry. RERA criteria should be sought if an observed event does not meet apnea or hypopnea criteria. RERA is defined as a sequence of breaths >10 seconds in duration that is associated with increased respiratory effort and results in an arousal from sleep. The American Academy of Sleep Medicine (AASM) directs that apneas, hypopneas and RERAs, if present, be scored in the routine PSG interpretation. The average number of apneas and hypopneas in 1 hour is referred to as the apnea-hypopnea index (AHI). But if RERAs are present, then the average number of apneas, hypopneas and RERAs should be calculated. This is the respiratory disturbance index (RDI). Note, AHI does not equal RDI, even though the terms are sometimes used interchangeably; such an interchange could create confusion.

27. What is the prevalence of OSA?

The prevalence is dependent on the definition of OSA. The earliest epidemiological investigations, primarily of white men, estimated that up to 4% had OSA (60%–90% were obese). The classic prevalence of OSA for adults age 30–60 years old now is *24% in men and 9% in women*. Obesity is a major risk factor. In nonobese patients, genetic craniofacial features like retrognathia (maxillary insufficiency) are correlated with OSA. As OSA data matures, the prevalence may become unique to populations or ethnicities. For example, in Asian nonobese male office workers, BMI and age were positively correlated, but weight was less so than in white, non-Asian subjects. Risk factors for OSA other than adiposity, such as pharyngeal narrowing, retrognathia or micrognathia, and pharyngeal collapsibility are thought to assume greater pathologic significance in Asians.

28. Define sleep deprivation. How common is it?

Sleep deprivation can be acute or chronic. By definition, going without sleep for 24 hours is total acute sleep loss, whereas sleeping less than 6 hours a night for six nights or greater is considered chronic sleep deprivation. People in industrialized nations are sleeping less. In the United States, for example, over 30% of adults less than 64 years of age report sleeping less than 6 hours per night, leaving no doubt that many patients are accumulating chronic sleep deprivation.

29. What are the key features of sleep deprivation versus sleep apnea?

In sleep deprivation, one does not sleep but breathes normally. In sleep apnea, one sleeps but doesn't breathe well during sleep. One can objectively measure excessive daytime sleepiness (EDS) with a standardized tool, such as the Epworth Sleepiness Scale (ESS). One must appreciate that this screening tool is specific but not sensitive. An ESS score > the 9–10 range is consistent with EDS, but not necessarily OSA. The greatest clinical use for this scale is serial tracking of patients in response to therapy. It is important to remember that the ESS does not correlate with: (1) objective testing for sleepiness; (2) likelihood of OSA on overnight PSG; and (3) the patient's perception of sleep-related problems. Patients with acute or chronic shortening of sleep resist the drive to sleep with no impairment of gas exchange. In OSA, there is a repetitive collapse of the upper airway, which induces apneic and hypopneic episodes despite persistent thoracic and abdominal respiratory effort. This leads to mechanical loading on the upper airway, chest wall, and diaphragm. What follows are hypoxia, hypercarbia, and a marked increase in SNS tone. OSA often leads to disruption or fragmentation of the usual sleep wake cycle and endocrine responsiveness. Both can contribute to fatigue and daytime sleepiness. In contrast, if EDS is secondary to sleep deprivation, the patient's sleep continuity is normal and is often associated with an increase in SWS.

30. In view of increased SNS tone in OSA (see Question 29), does the comorbidity of OSA interfere with the assessment of metanephrines and catecholamines when screening for pheochromocytoma?

Yes. OSA results in an appropriate release of catecholamines in response to physiologic stress or disease, just as myocardial infarctions, cerebral vascular accidents, and acute heart failure are associated with appropriate acute catecholamine increases. If a 24-hour urinary collection is performed in the setting of undiagnosed or poorly treated OSA, it would likely contain elevated metanephrine and catecholamine levels. This may falsely suggest a diagnosis of heochromocytoma.

31. What endocrine diseases are associated with OSA?

The endocrine diseases commonly associated with OSA are *hypothyroidism*, *acromegaly* and *polycystic ovary syndrome (PCOS*), but the most prevalent are *obesity* and *T2DM*. As would be expected, the statistics for these disorders vary according to the series. Although it was once thought that all OSA patients had subclinical hypothyroidism, this has now been shown not to be the case. In general, 11%–30% of patients with OSA will have subclinical or overt hypothyroidism and the prevalence of OSA in hypothyroid patients is about 30%. OSA is reversible in the majority of such patients once they are treated appropriately with thyroid hormone replacement. In one prospective study of nonobese, middle-age men and women with newly-diagnosed symptomatic hypothyroidism, 30% had OSA by PSG at study onset; 84% of those subjects had reversal of OSA with TSH normalization. Finally, insulin levels and measures of glucose tolerance in PCOS are strongly correlated with the risk and severity of OSA. Additionally, among those PCOS women with normal glucose tolerance, insulin levels are significantly higher in those at high versus low OSA risk, independent of body mass index. Therefore, it is reasonable to assess measures of sleep habits and behaviors, and restorative sleep in all PCOS patients. Probably the most alarming statistics are the prevalence of obesity and its partner in crime, T2DM. Using the older OSA diagnostic criteria, the prevalence of moderate to severe OSA in obese women and men <65 years, was 4%–7% and 9%–14%, respectively. More recent studies, using current diagnostic definitions, reported a substantially higher prevalence of moderate to severe OSA of 23% in obese women and 49% in obese men.

32. How is the sleep apnea of GH excess different from the sleep apnea of thyroid hormone deficiency?

GH excess is associated with a high proportion of obstructive and central sleep apnea, while hypothyroidism is almost uniformly associated with OSA. Up to 60% of acromegalics are eventually found to have sleep apnea by PSG studies. In one series, over 30% had central sleep apnea. Endoscopy revealed little occlusive posterior tongue movement during sleep, indicating that this is not from macroglossia. The mechanism for central sleep apnea in acromegalic patients is not clear.

33. How does sleep deprivation influence glucose tolerance?

In one study, after one week of sleeping 4 hours per night, there were increases in postbreakfast insulin resistance. During sleep restriction, glucose tolerance is nearly 40% worse when compared to a group with sleep extension. Interestingly, it is first phase insulin release that has been found to be markedly reduced. When sleep deprived individuals go into recovery sleep (sleeping during the day due to prior sleep deprivation), there are marked elevations of glucose and insulin levels, indicating that sleep also exerts modulatory influences on glucose regulation independent of the circadian rhythm.

At this point it is important to reference a recent meta-analysis of 36 studies, investigating risks of developing T2DM. The study incorporated over one million patients, to quantify the relative contribution of sleep disturbances with traditional T2DM risk factors. The relative risk of T2DM development is within parenthesis, and in descending order: overweight (2.99) > family history of T2DM (2.33) > personal history of OSA (2.02) > nightly sleep less than 5 hours (1.48) > shift work or sleeping greater than 9 hours or the independent characteristic of poor sleep quality (1.4) > physical inactivity (1.2).

34. What sleep abnormalities are associated with abnormal glucose metabolism? Snoring, sleep duration, and *OSA* have all been linked to hyperglycemia and T2DM risk.

- **Interestingly just *snoring*,** in nonobese Asians and especially in those who are obese, has been independently associated with abnormal oral glucose tolerance tests and higher HbA1c levels.
- **In epidemiologic studies, *sleep duration*** has been both negatively and positively correlated with the risk of developing T2DM. Observational studies have shown that patients who report less than 6 hours of sleep per night have an increased prevalence of glucose intolerance and T2DM. Very recently, it was found that the duration of sleep (<6 and >8 hours per night) was predictive of an increased incidence of T2DM.
- ***OSA*,** as diagnosed by PSG, is independently associated with abnormal glucose metabolism. A recent study extends this independent association through rigorous assessment of the potential confounders of overweight/obesity. In this cross-sectional analysis of 2588 patients, it was shown that impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and occult diabetes are associated (but to different degrees) with OSA in both the normal-weight (BMI < 25 kg/m^2) and overweight/obese subgroups. This suggests that individuals with OSA are at special risk for T2DM. Importantly, sleep fragmentation and hypoxemia are likely OSA culprits leading to hyperglycemia. A 2009 study comparing nondiabetic subjects without OSA to nondiabetic patients with mild, moderate, and severe OSA showed 27%, 37%, and 44% decreases, respectively, in insulin sensitivity due to OSA; this contribution to reduced insulin sensitivity was found to be independent of age, gender, ethnicity, and percent body fat. Further there were no increases in insulin concentrations. Unfortunately, at present the relative contributions of sleep restriction, sleep fragmentation, and hypoxia cannot be ascertained. The risk of hyperglycemia is likely proportional to OSA severity; data from diverse patient populations suggests that OSA severity is a risk for T2DM development. The prevalence of OSA in patients with T2DM is 60%–80% based on an evaluation of 12 clinic or community-based cohorts from 2003–16. The prevalence of T2DM in patients with OSA is reported to be 15%–30%.

35. What are the main mechanisms underlying the development abnormal glucose metabolism in sleep apnea patients?

The hallmark of OSA is airflow reduction, which is typically associated with intermittent hypoxemia, sleep fragmentation and SNS stimulation. In animal studies, insulin sensitivity has been shown to vary with intermittent hypoxemia, independent of activation of the SNS. Additionally, it has been shown that in nondiabetic overweight to mildly obese males, every 4% decrease in oxygen saturation is associated with an odds ratio that approaches 2.0 for abnormal glucose tolerance. Sleep fragmentation has also been associated with abnormal glucose metabolism. In one study of *healthy* adults, selective suppression of SWS (without decreasing total sleep time) was associated with decreases in insulin sensitivity of nearly 25%! This suggests that the low levels of SWS in the sleep restricted, the elderly and obese subjects may contribute to their increased incidence of T2DM. In a study of consecutive adults with T2DM (age: 41–77 years, BMI 20–57 kg/m^2), mild OSA was associated with a mean HbA1c of 7.22% and severe OSA with a HbA1c of almost 9.42%. After adjustments for age, gender, race, BMI, number of diabetic medications, level of exercise, years of diabetes and total sleep time, the severity of OSA by AHI correlated significantly with higher mean HbA1c values.

36. With respect to causality, does the use of CPAP improve abnormal glucose metabolism parameters?

Yes. This is seen in nondiabetic subjects, in nonobese diabetic patients and in patients with poorly controlled diabetes. *Caveat: in this body of work, the reader must discern from the trial whether or not there was a published measure of CPAP compliance and, when subjects were compliant with CPAP, how effective the treatment was in normalizing events. Likely the study group that will get maximum benefit is the one with normalized sleep (duration > 7 hours, with residual AHI < 5 events/hour).*

Trials reporting CPAP adherence definitions and those demonstrating no change in BMI during the study period do show improvement. A study of nondiabetic patients with moderate to severe OSA reported that CPAP significantly improved insulin sensitivity after only 2 days of treatment and that the improvement persisted at the three-month follow-up with no significant changes in body weight. Interestingly, this benefit was most pronounced in nonobese subjects. In contrast, the same research lab showed no improvement in insulin sensitivity in obese T2DM patients. In other trials, *postprandial blood glucose levels improved most significantly after CPAP use* in patients with T2DM and OSA.

Overall OSA treatment in diabetes patients translated to a mean decrease in HbA1c of 0.4% (from 8.4% to 8.0%). The CPAP influence was larger in those with higher initial HbA1c values. In one trial of consecutive patients with poorly controlled T2DM (HbA1c > 8.5%) and moderate or severe OSA (undiagnosed/or known but not untreated), normalization of respiratory events translated to a mean decrease in HbA1c of 0.9%. This is respectable T2DM therapy since most current T2DM medications lower HbA1c roughly 0.5% to 1.5%.

Therefore, one can say that for the price of a good night of sleep, the diabetic patient is likely also to achieve glycemic improvement. Naysayers would argue that while this benefit is reported, it is likely offset by weight gain from CPAP therapy. However, in the randomized controlled trials that addressed this question, there was no change in body composition; furthermore, daytime sleepiness improved and physical activity increased over a 3-month period. It is reasonable to conclude that the use of CPAP is at least weight neutral, but this issue remains under investigation. There remain concerns that the decreased work of breathing with CPAP and the improved GH secretion associated with restoration of sleep architecture may increase the tendency to gain weight (see Question 38).

37. How well are providers in diabetes clinics screening their patients for OSA? What are good tools for screening by history and physical exam?

A study of diabetic patients, using a validated questionnaire to quantify OSA risk and sleepiness, revealed that 56% of patients reported snoring, 29% had fatigue upon awakening, and 34% reported feeling tired during wake time. The authors of the study concluded that 56% of those questioned were at high risk for OSA. This finding supports a call for greater vigilance in screening for OSA in patients with diabetes given the high prevalence of SDB found in this patient population. Certain screening tools may be helpful towards this end. BMI is proportional to OSA risk. Neck size greater than 17 inches is the most sensitive physical finding. Some craniofacial changes, such as retrognathia, also place a patient at high-risk. Keep in mind that a patient with OSA is often unaware of the neurocognitive changes that have developed slowly over time, and thus he or she may not volunteer a history consistent with OSA unless directly queried.

38. Does the effective use of CPAP in OSA patients lead to weight loss?

Results are not consistent on this matter. Some 30% of treated OSA patients may have stable or even increased body weight, with two mechanisms having been implicated: (1) decreased work of breathing with treated OSA translates to conservation of calories during sleep and (2) improved sleep architecture leads to increased SWS and, therefore, increased GH secretion with attendant weight gain. For those that lose weight, two distinct mechanisms have also been proposed. First, patients with treated OSA usually wake more rested and with a sense of improved vitality or energy; once on treatment, OSA patients have even been shown to exercise more. Second, treatment of OSA results in normalization of serum leptin (from the Greek word *leptos*, meaning "thin"), the so-called satiety hormone. As will be discussed below, leptin is suppressed during sleep deprivation and in untreated sleep apnea.

39. What are the effects of sleep deprivation on leptin (satiety hormone) and ghrelin (hunger hormone)?

With sleep deprivation, leptin decreases and ghrelin (from the original root *ghre* meaning "to grow") increases. In longer than average sleep, leptin increases and ghrelin decreases. It has been documented that leptin secretion is blunted in sleep deprived subjects and that over a 6-month period of time sleep deprived subjects gain an average of 10 pounds more than rested subjects.

40. How does the testosterone panel change with OSA? Does OSA treatment influence the panel?

The androgen changes of OSA are distinct from those seen with aging and obesity (e-Table 75.3). In OSA, there are decreases in serum total and free testosterone and sex hormone binding globulin (SHBG) levels without concomitant gonadotropin increases. In fact, one study showed LH pulse disturbances with untreated OSA. Interestingly, testosterone levels improve with OSA treatment, whether by CPAP or with uvulopalatopharyngoplasty (UPPP). These findings point to a hypothalamic mechanism for low testosterone levels in untreated OSA.

41. How does androgen replacement therapy influence sleep?

Exogenous testosterone may worsen existing OSA or lead to changes associated with OSA. One randomized controlled trial revealed that high dose testosterone administration in hypogonadal, otherwise healthy, elderly men shortened total sleep time and worsened coexisting undiagnosed sleep apnea. Though there have been no substantiated reports of decreased cognition and impaired driving ability with hypogonadism, *it is incumbent on the prescriber to screen patients for the possibility of undiagnosed OSA before prescribing androgen replacement therapy.*

42. How does one tease out the possible primary contribution of a sleep abnormality in a fatigued patient?

Some illustrative examples will be useful. A female patient complains of fatigue and believes it must be due to a thyroid problem; and a male patient has similar complaints and attributes his fatigue to low testosterone. The following is presented to allow the clinician to pick and choose an individualized approach to each specific patient.

- **First,** differentiate whether there is an element of sleepiness to what a patient means by "fatigue"; i.e., seek to distinguish, if possible, fatigue and sleepiness. Fatigue and sleepiness may mean the same thing to our patients. However, fatigue is usually felt after prolonged exertion or hard physical work. Patients may have a sense of not feeling themselves, decreased efficiency, loss of power, and even loss of responsiveness to stimulation. If the fatigue has an element of sleepiness, however, this may be historical evidence that the primary complaint is actually sleepiness. Such a patient usually has deficient sleep duration and/or disrupted sleep (insomnia, untreated OSA, or restless leg syndrome), may admit to sleepiness upon awakening despite >7 hours of apparent sleep time and/or difficulty staying awake in the late morning, afternoon or with family in evening.
- **Second,** use a basic sleep history to implicate a problem with sleep habits that might provide a clue to sleep pathology. The average adult should be getting at least 7 hours of consolidated

E-TABLE 75.3 Androgen changes in common circumstances

CONDITION	SHBG	TOTAL TESTOSTERONE	FREE TESTOSTERONE
Aging	↑	↓	↓
Obesity	↓	↓	Normal
OSA	↓	↓	↓

OSA, obstructive sleep apnea; *SHBG*, sex hormone–binding globulin.

sleep with <20–30 minutes to get to sleep and <20–30 minutes of awake time after they initially achieve sleep. Are the time they go to bed and the time they are asleep and their wake time usually consistent? Do they have the typical features of sleep disordered breathing; for example, do they wake up frequently during the night, often for reasons unknown, sometimes snoring themselves awake? Are there unprovoked sweating episodes and are there awakenings consistent with hot flushing (which may also happen during the day)? Do they have increased heartburn at night? Is there increased movement or fitful sleeping, such as moving back and forth or finding the bed covers helter-skelter in the morning? Does their partner complain of loud snoring or breath holding? Is there difficulty with leg movement or features of a clinical diagnosis of restless leg syndrome (RLS)? The mnemonic for RLS is "URGE," **U**rge to move legs (can only be ill-defined leg discomfort), worse with **R**est, better if the patient **G**ets up and walks around, and finally worse in **E**vening).

- **Third,** use the screening tools for sleepiness and for risk of occult OSA. Use the ESS (see Question 29) for assessment of daytime sleepiness, remembering this tool is specific and not sensitive; a score in the 9–10 range warrants further review of the sleep history (though not necessarily a sleep study). Additionally, one can screen for the risk of sleep apnea using the **STOPBANG** mnemonic. Snoring loudly (louder than usual speech, or heard behind closed doors), **T**ired during the day, **O**bserved apneas, **P**ressure-treated for hypertension, **B**MI > 35 kg/m2, **A**ge > 50 years old, **N**eck Circumference > 16 inches (40 cm); **G**ender male; (each parameter = 1 point). The total score is used to predict risk of OSA: low risk 0–2; intermediate risk 3–4; high risk 5–8.
- **Fourth,** use the physical exam to look for features that may worsen collapsibility of the already malleable ADULT posterior oropharynx (OP) during sleep. *Recall, it is only the airway segment below the jaw angle and above the manubrium, that does not have anatomical buttressing and is, therefore, vulnerable to nighttime narrowing.* So, look for anything in the OP that can impact this dynamic. For example, examine the overall anterior perspective of the OP for these features: **narrow jaw** (high arched palate, teeth crowding); **septal deviation**; **insufficiency of the mandible;** so called **receding chin** with attendant **maxillary overjet**. For example, is there ≥3–5 mm space between the posterior surface of the maxillary incisors and the anterior surface of the mandibular incisors? If so, this could indicate a narrowed OP. Another related tip, check for mandibular insufficiency (i.e., protrusion of the maxillary incisors, aka "buckteeth"). From a sideview of the face, maxillary insufficiency gives the patient a flat to concave facial profile; these patients can also have a smaller zygomatic arch. With the mouth open assess tonsil size. Tonsillar enlargement is graded as follows: Grade 0, tonsils are *absent*; Grade 1, tonsils *hidden behind* tonsillar pillars; Grade 2, tonsils *extend to* pillars; Grade 3, tonsils *visible beyond* pillars; Grade 4, tonsils *enlarged to midline.* With the mouth still open and the patient seated, inspect the OP directly. Ask her/him to protrude the tongue. The following assessment is the Mallampati classification. Class I: all of the following are visible—the soft palate, uvula, tonsillar columns (anterior and posterior) and fauces (the passage from mouth to throat, anterior boundary behind and lateral to uvula); Class II: uvula, soft palate, and fauces are visible but tonsillar pillars are not visible; Class III: soft palate, fauces, and only the base of uvula are visible; and Class IV: soft palate no longer visible, nor are the fauces, uvula, or tonsillar pillars.

KEY POINTS

Sleep and Endocrinology

- Sleep-wake regulators and neuroendocrine controllers are co-located in the hypothalamus and are responsible for functional integration to accomplish and protect homeostasis; this likely underlies the overlap of sleep maladies and endocrine disorders.
- The endocrine diseases associated with abnormal sleep include: type 2 diabetes mellitus, obesity, acromegaly, hyperthyroidism, hypothyroidism, and polycystic ovarian syndrome.
- Normal sleep preserves normal 24-hour hypothalamic-pituitary-hormone axis cycling for several hormone systems. Sleep deprivation and OSA can impair hormone cycling.
- Mechanisms responsible for 24-hour hypothalamic-pituitary-hormone cycling are circadian, sleep-wake homeostatic, or both. These mechanisms are complex, distinct, and superimposed on classic hormonal feedback loop mechanisms.

- The master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which relays an intrinsic rhythm to peripheral organ systems using genetic clockwork: two positive loop genes are CLOCK and BMAL1 and two negative loop components are PER and CRY.
- Current evidence links the circadian system to diabetes pathophysiology and treatment.
- States of sleep and wake are best conceived of as flip-flops switches. Transitioning from sleep to wake is accomplished by the reticular activating system (RAS) and is composed of a series of cortical-activating nuclei with multiple neurotransmitters. The transition from wake to sleep is accomplished by one neurotransmitter, γ-aminobutyric acid (GABA).
- Sleep architecture changes with aging to consist of less total sleep time and less SWS.
- OSA requires polysomnography (PSG) for diagnosis.
- Acute sleep loss eliminates the normal nocturnal suppression of TSH secretion.
- Sleep deprivation disrupts SWS resulting in a decrease in levels of the hormones that are entrained to SWS (GH and PRL).
- Short-term sleep deprivation increases serum cortisol levels, suppresses insulin secretion and diminishes glucose tolerance. It also decreases serum leptin and increases ghrelin levels such that sleep deprived subjects gain weight compared to nonsleep deprived subjects.
- OSA results in less predictable hormone changes depending on the extent of sleep fragmentation, elevation of adrenergic tone, and hypoxia. It is associated with decreased insulin sensitivity and worsened glucose tolerance proportional to the severity of OSA, and inversely proportional to the time amount of CPAP use.
- Effective treatment of OSA improves sleep architecture, normalizes hormone release, and improves abnormal glucose metabolism.
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WEBSITES

Sleep Research Society http://www.sleepresearchsociety.org/
NIH, NHLBI, National Center on Sleep Disorders Research http://www.nhlbi.nih.gov/about/ncsdr/index.htm
American Academy of Sleep Medicine http://www.aasmnet.org

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